VOLUME 83 NUMBER 1

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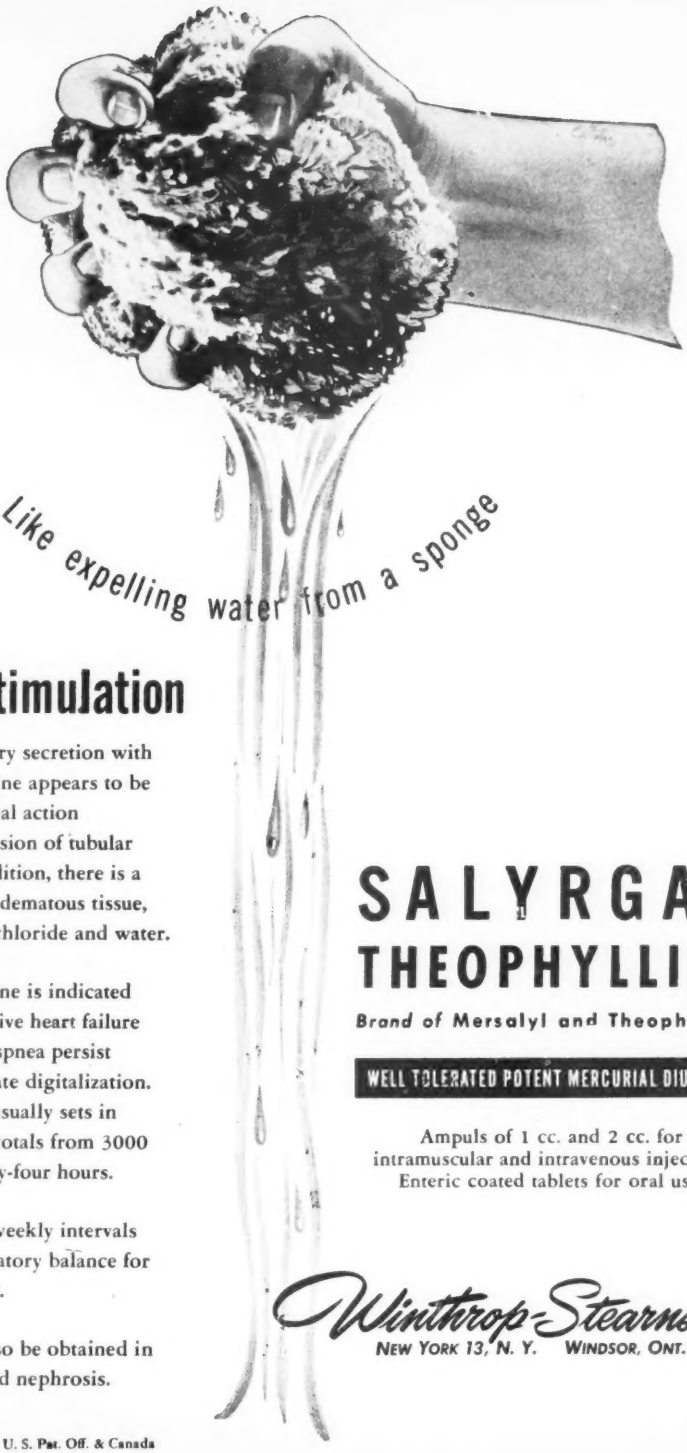


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*Beams, A. J., and Endicott, E. L., Histologic changes in the livers of patients with cirrhosis treated with methionine, Gastroenterology 9:718-735 (Dec.) 1947.

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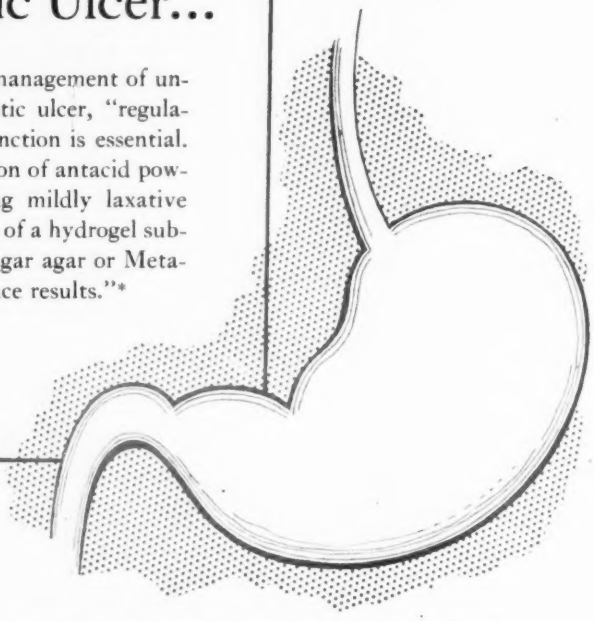

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*Gerendasy, J.: Modern Treatment of Peptic Ulcer, J. M. Soc. New Jersey *43*:84 (March) 1946.

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# PATHOGENESIS OF SO-CALLED DIFFUSE VASCULAR OR COLLAGEN DISEASE

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PITTSBURGH

WITHIN the last two decades, there have been many attempts to correlate various systemic diseases that have shown vascular lesions. Among these have been periarteritis nodosa, disseminated lupus erythematosus, thromboangiitis obliterans, scleroderma, rheumatoid arthritis, rheumatic fever, dermatomyositis, verrucous endocarditis and serum sickness.

In our studies of postmortem and biopsy specimens, we observed certain changes involving the vessels and the collagenous tissue in the aforementioned diseases. These changes, however, were also noted in routine autopsies on patients whose conditions were not diagnosed as any of these. It is our purpose in this paper to point out certain similarities pathologically in these diseases and in the normal aging processes. Further, we will attempt to point out that this "accelerated aging" process of the vessels primarily and of the collagenous tissue secondarily is the basis of the pathogenesis of the so-called diffuse vascular or collagen diseases.

In our discussion, we propose the term "panarteriolitis" to describe the process, acute or chronic, involving the entire wall of small and medium-sized blood vessels and the vasa vasorum of larger blood vessels. The terms "fibrinoid" or "collagenous" degeneration refer to the chronic healing changes in the involved vessels. These, of course, are not clinical or pathologic entities but rather various stages of response to miscellaneous toxic substances.

## REPORTS OF CASES

CASE 1.—*Lupus Erythematosus.*—F. S., a 25 year old white woman, was admitted to the hospital on Nov. 2, 1946, with the chief complaint of "rash on the face, neck and upper arms." Two months previous to admission, this patient first noted an erythematous lesion on the face, which spread in a butterfly fashion across the bridge of the nose and both cheeks. About one month before admission

From the Department of Pathology Montefiore Hospital.

the lesion became more diffuse over the face and neck; this followed a treatment with ultraviolet rays. The lesion became scaly and extended to the proximal portion of the thumb, and to the ventral surfaces of both arms. These lesions were erythematous and papular. The patient had a persistent elevation in temperature (100 to 101 F.) and slight pruritis over the involved areas.

Past medical history revealed the usual childhood diseases and one normal delivery. The family history was essentially noncontributory. The patient had been married for five years, and had 1 child living and well. She did not smoke or

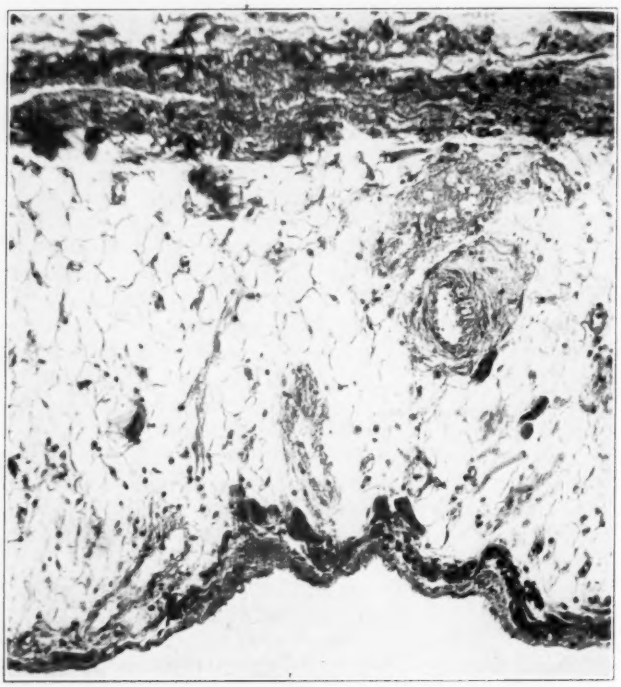

Fig. 1.—Lupus erythematosus. Section of the skin showing pronounced degeneration and atrophy of the stratified squamous epithelium with ulceration and desquamation, some fibrinoid degeneration of the deeper blood vessels and round cell infiltration; × 140, hematoxylin and eosin.

drink alcoholic beverages. She had spent the last year in Florida and was "sunburned" severely.

Examination of the head and neck revealed photophobia, which had become more noticeable of late. Several episodes of epistaxis had occurred in the past six months and a sore throat more recently. Respiratory, cardiovascular, gastrointestinal and genitourinary systems and menses were otherwise normal.

*Physical Examination.*—Examination revealed a well developed, white woman, 25 years of age, appearing chronically ill. A severe erythematous, edematous, excoriated, coalescent dermatitis involved the face, neck and upper extremities. A large bullous lesion was present on the right side of the neck. The skin was warm and dry. The scalp revealed some exfoliative areas. The eyelids were edematous and involved in the erythematous process. There was some purulent exudate on the conjunctivas. The pupils were equal and reacted to light and accommodation. The extraocular movements were normal. The nose showed evidence of recent bleeding and the mouth was normal. A large bullous lesion with a red hyperemic base was present on the neck. The lungs were clear to percussion and auscultation. The blood pressure was 120 systolic and 70 diastolic. Heart sounds were of good quality; no enlargement or murmurs were present, and the pulse was regular. The abdomen showed old striae; no viscera were palpable. Discrete erythematous papules on the ventral surface of the arms were noted.

*Laboratory Findings.*—Urinalysis showed $p_H$ of 6.5; the specific gravity was 1.021 to 1.016; the reaction for albumin was 1 to 2 plus. No sugar was present. Microscopic examination showed occasional red and white blood cells. The hemoglobin concentration was 77 per cent; red blood cells numbered 3,400,000 and white blood cells, 9,350 to 4,800, with 69 polymorphonuclear leukocytes and 31 lymphocytes. The sedimentation time (Litzenmeier) was 29 minutes.

*Course in the Hospital.*—The patient showed a low grade elevation in temperature, 100 to 101 F., for ten days. This gradually disappeared. Treatment consisted of liver extract administered intramuscularly and 50 mg. of diphenhydramine (benadryl®) hydrochloride every six hours. No local applications were given other than boric acid compresses to the eyes. Her diet was free from salt and green vegetables. She improved slightly and was discharged from the hospital November 22.

The patient was readmitted to the Rochester General Hospital, Rochester, Pa., in July 1947, in a comatose state, and she died July 30. Autopsy was performed by Dr. T. W. McCreary. The anatomic diagnoses were: disseminated lupus erythematosus; subacute glomerulonephritis; atelectatic pneumonitis with bronchopneumonia; passive congestion of liver and spleen, and generalized panarteriolitis.

*Comment.*—In disseminated lupus erythematosus, the vascular lesions are generally limited to arterioles and capillaries. This vascular concept was revealed by Keil.[1] One can see all the stages of inflammation and healing in the same organ; Klemperer and his co-workers,[2]

1. Keil, H.: (*a*) Conception of Lupus Erythematosus and Its Morphologic Variants, Arch. Dermat. & Syph. **36**:729 (Oct.) 1937; (*b*) Manifestations in the Skin and Mucous Membranes in Dermatomyositis, with Special Reference to the Diagnosis from Systemic Lupus Erythematosus, Ann. Int. Med. **66**:643, 1940; (*c*) Relationship Between Lupus Erythematosus and Tuberculosis: A Critical Review Based on Observations at Necropsy, Arch. Dermat. & Syph. **28**:765 (Dec.) 1933.

2. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569 (Oct.) 1941; Diffuse Collagen Disease: Acute Disseminated Lupus Erythematosus and Diffuse Scleroderma, J. A. M. A. **119**:331 (May 23) 1942; On the Nature of Acute Lupus Erythematosus, New York State J. Med. **42**:2225, 1942.

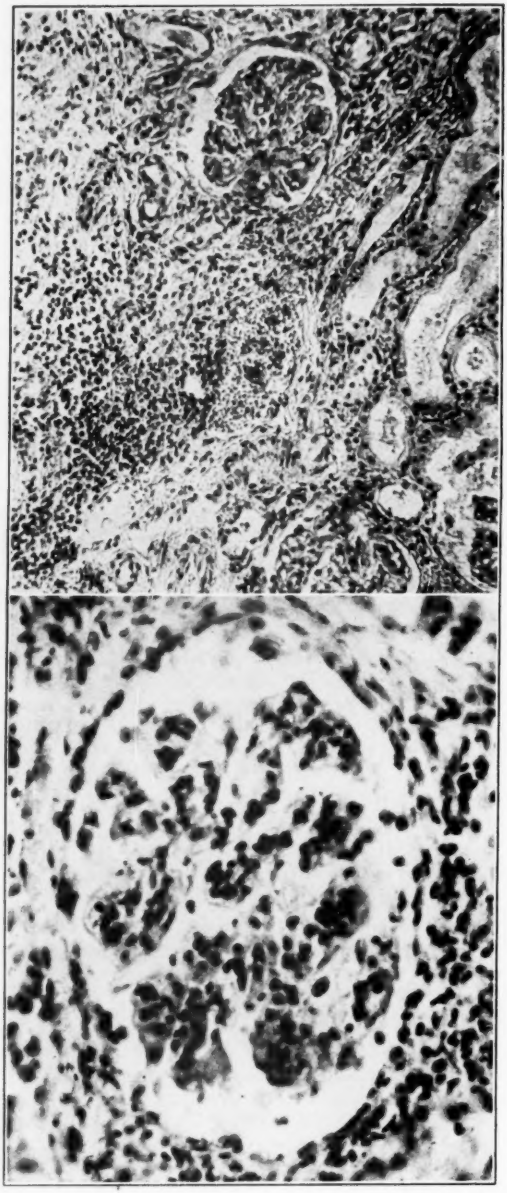

Fig. 2.—Lupus erythematosus. The upper part shows thickening and hyalinization of the loops of capillaries of the glomerular tufts and also areas of round cell infiltration, interstitial spaces and pericapillaries; × 140, hematoxylin and eosin. The lower part shows a damaged tuft with so-called wire loop degeneration; × 900, hematoxylin and eosin.

however, stressed involvement of systemic collagen. Besides the cutaneous lesions, the organs commonly involved in this disease are the kidneys, myocardium, endocardium, lungs and liver. According to Baehr and Pollack,[3] the most characteristic of all the lesions of the kidney is the so-called wire loop necrosis of the glomerular tufts. There is also leukocytic infiltration, a lesion resembling that seen in periarteritis nodosa. These types of lesions were described by Fox.[4] The lymph nodes may occasionally show giant cells and fibrinoid degeneration of the germinal centers. This point was emphasized by Foldes.[5] Occasional

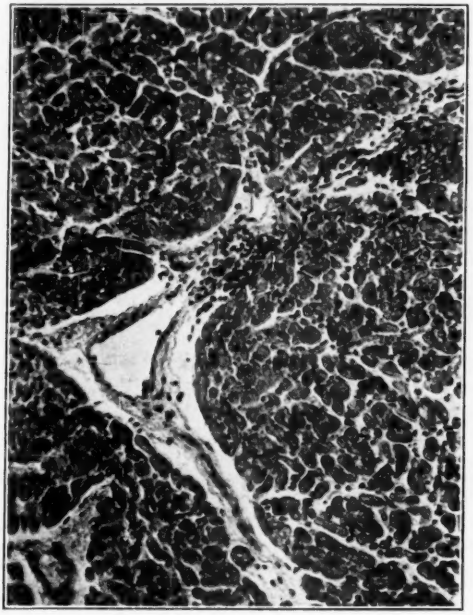

Fig. 3.—Lupus erythematosus. Section of the myocardium with perivascular round cell infiltration; × 140, hematoxylin and eosin.

eosinophilic infiltration may also be seen, which suggests allergy as the causative factor.

3. Baehr, G., and Pollack, A. D.: Disseminated Lupus Erythematosus and Diffuse Scleroderma, J. A. M. A. **134**:1169 (Aug. 2) 1947.

4. Fox, R. A.: Disseminated Lupus Erythematosus—An Allergic Disease? Arch. Path. **36**:311 (Sept.) 1943.

5. Foldes, J.: Acute Systemic Lupus Erythematosus, Am. J. Clin. Path. **16**:160, 1946.

We should like to point out that the clinical lesions of lupus erythematosus can easily be explained by diffuse vascular lesions. This is characteristically demonstrated in the "wire loop" capillaries. The cutaneous lesions, too, are predominantly vascular. Secondary hyalinizing changes should not obscure recognition of the vessel as the primary battleground in this disease. Because a "fibrinoid" degeneration has taken place does not in any way invalidate the fact that the lesion is primarily occurring in a vessel.

The acuteness of the disease and the intensity of the etiologic stimulus are responsible for the differences pathologically between lupus and the changes seen in the usual arteriosclerotic aging process.

CASE 2.—*Rheumatoid Arthritis.*—L. M., a 43 year old white woman of Jewish descent, was admitted to the hospital on May 17, 1946, with the chief complaints of cough, pain in the chest and vomiting. The patient was perfectly well until November 1944, when, following exposure and severe shock caused by a fire at her home, she had a severe infection of the upper respiratory tract with migrating pains and swelling in the joints which persisted intermittently until the spring of 1945. Since that time, pains in the joints had recurred on occasion. The patient was well again until December 1945, when there was a sudden onset of chills, fever, weakness and severe, unproductive cough. The cough occurred in paroxysms, was accompanied with abdominal pain (due to cough) and was occasionally followed by vomiting. She was in bed from six to eight weeks, during which time she vomited intermittently after meals. There was progressive loss in weight (40 pounds [18.1 Kg.] in four months), weakness and fatigue. No hemoptysis was noted.

Her past medical history revealed two normal deliveries and an appendectomy.

The patient had had occasional headache and slight dizziness. Slight exertional dyspnea and edema of the ankles were present. No dysuria or hematuria was noted. The menses had stopped abruptly in March 1946 and were now irregular. Occasional pains in joints were reported.

*Physical Examination.*—The patient was a pale, white woman who appeared much older than the stated age and was dehydrated. The skin was warm and dry. The head and neck showed no abnormality; no adenopathy was palpable. The lungs were clear to percussion and auscultation. The blood pressure was 115 systolic and 70 diastolic. The loudest precordial sound was heard in the fifth interspace in the midclavicular line. There were no enlargements or murmurs. Abdominal examination revealed nothing abnormal. The extremities showed bilateral edema (2 plus) of the ankles, slightly more on the right. The patient had a firm nodule on the left sacral region. The pelvic organs were essentially normal except for slight enlargement of the uterus. There was a generalized sparsity of hair, which had been falling out continuously since the onset of the illness.

*Laboratory Examination.*—Urinalysis revealed a 2 to 3 plus reaction for albumin. The test for sugar had a negative reaction. White blood cells ranged from 3 to 6, and red blood cells from 10 to 15 per high power field. Many hyaline and finely granular casts were present. Reaction to the Bence Jones test for protein was negative. The hemoglobin concentration was 57 per cent. Cell count showed 3,100,000 red blood cells and 5,600 white blood cells, with 79 polymorphonuclear leukocytes and 21 lymphocytes. Sedimentation time (Litzenmeier) was 10 minutes. Wassermann and Kahn tests showed negative reactions.

The basal metabolic rate was + 16 per cent. Nonprotein nitrogen measured 23 mg.; creatinine, 1.0 mg.; serum protein, 6.11 Gm. and 7.4 Gm.; albumin 3.03 Gm., and globulin, 3.08 Gm., per hundred cubic centimeters. Alkaline phosphatase was 3.6 Bodansky units and in the phenolsulfonphthalein test 4 per cent of the dye was excreted. Roentgenograms of the chest, heart and lungs, lumbar portion of the spine, sacroiliac region and pelvis showed nothing abnormal. Administration of a barium sulfate meal and enema revealed the stomach, duodenum and colon to be normal. Roentgenograms of the skull and sella turcica showed no changes.

*Course in the Hospital.*—The patient had a low grade fever (99 to 101 F.) during her stay in the hospital. She complained on several occasions of severe epigastric pain radiating to the arms, back, ribs and substernal region. Examination revealed nothing during these episodes. She was discharged on June 18 without improvement after therapy consisting of blood transfusions and administration of liver extract, vitamins, estrogenic substances and anterior pituitary injection.

The patient was readmitted on Jan. 4, 1947, with the chief complaints of pain in the chest and swelling of the ankles. Her chronic, unproductive cough had persisted. The substernal pain was unrelated to effort and had none of the anginal characteristics. Slight exertional dyspnea was present. There was neither orthopnea nor hemoptysis. Ten more pounds (4.5 Kg.) had been lost in the interim. Edema of the ankles had become severe and more persistent, and weakness was pronounced. There had also been marked frequency of micturition and nocturia (five to six times a night), but this was of inconstant occurrence. Menstrual bleeding had completely stopped.

*Physical Examination.*—The patient was a thin, pale, white woman of 45, appearing lethargic. Examination continued to show nothing abnormal. The blood pressure was 126 systolic and 74 diastolic; the pulse was 88 per minute. No viscera were palpable. There was bilateral edema of the legs (4 plus). A maculopapular rash was present on the right forearm.

*Laboratory Examination.*—Urinalysis showed specific gravity of 1.003. Reaction for albumin was 1 plus and no sugar was detected. Microscopic examination revealed occasional white and red blood cells. The hemoglobin concentration was 80 per cent. Red blood cells numbered 3,800,000 and white blood cells 5,650, with 77 polymorphonuclear leukocytes and 23 lymphocytes. Nonprotein nitrogen measured 38 mg. per hundred cubic centimeters. Mosenthal's test for kidney function resulted in specific gravities of 1.015 to 1.020, the greatest value occurring in the sample taken at night. The dextrose tolerance test gave normal results. Whole blood chloride measured 498 mg. per hundred cubic centimeters. The chest appeared normal on roentgenogram. The electrocardiogram showed no abnormality.

*Course in the Hospital.*—The patient had a low grade fever (from 99 to 100 F.). She refused to permit a biopsy specimen to be taken from a muscle. She received blood transfusion and was then discharged from the hospital, on January 20.

*Final Admission.*—The patient was last admitted on January 30 in a comatose state. She had been perfectly well at home until the morning of admission when she was found in a generalized convulsive state. The head and eyes were turned upward; the mouth was foaming. Respirations were rapid and shallow, and the arms and legs were in a state of myoclonic tremor. There was slight cyanosis.

Physical examination revealed a thin, white, 46 year old woman in a comatose state, incontinent of urine and feces. The eyes were open and moving pointlessly about. The skin was cold and cyanotic, and the tongue was dry and coated.

There was suggestive nuchal rigidity. Chvostek's sign was not elicited. The chest revealed occasional crackling rales at the bases of the lungs. The blood pressure was 70 systolic and 0 diastolic; heart sounds were weak and distant, and the pulse rate was 96 per minute and regular. The abdomen was normal. Reflexes were present and equal. The Kernig sign was suggestive bilaterally. The patient had two convulsions at one-half hour intervals. She then lapsed into deep coma. Her temperature was 106 F. and the pulse rate was 130 per minute. She died early in the morning of February 1. An autopsy was performed.

Spinal tap showed 200 mm. of water pressure. The fluid was clear and colorless. There were 10 to 15 cells per cubic centimeter. Urine showed a 4 plus reaction for albumin. Occasional white blood cells and 6 to 8 red blood cells were seen per high power field. There were many finely and coarsely granular casts. The hemoglobin concentration was 11 Gm. There were 4,200,000 red blood cells and 24,500 white blood cells, with 83 polymorphonuclear leukocytes and 17 lymphocytes. Nonprotein nitrogen was 55 mg. and creatinine 1.1 mg. per hundred cubic centimeters.

*Autopsy Observations.*—Postmortem examination showed adhesive pericarditis with recent hemorrhage, coronary arteriosclerosis, adhesive pleurisy and hypostatic congestion of the lungs, hepatomegaly, perisplenitis and septic splenitis, hemorrhagic gastritis, hemorrhagic nephritis, edema of the brain and emaciation. Histologic studies revealed chronic rheumatic pneumonitis, with pleural thickening and adhesions; acute myocarditis with focal necrosis; rheumatic pericarditis; focal interstitial nephritis; perihepatitis and perisplenitis, and passive congestion of spleen and liver.

*Comment.*—This condition is allied to the diffuse vascular or collagen disease and particularly involves the serous membranes, blood vessels, synovia of the joints and striated muscles. Recently, involvement of the skeletal muscles with perivascular round cell infiltration has been reported.[6] Herein, we believe, lies the clue to the pathogenesis of this disorder. This early evidence of diffuse vascular disease cannot be refuted. The collagenous end result, which is often observed in autopsy material, is but the final scarred picture in the story of repeated insult to and healing of vessels. The peculiar predilection for serous membranes and synovia is perhaps due to the constant stress and strain to which these structures are normally subjected. Clinically, the disease is extremely chronic, with stages of remission and exacerbation. Because at autopsy thickened serous membranes and scarred parenchymatous organs are observed, it is not entirely valid to conclude that these are typical lesions, since it is only the severer and chronically recurrent cases which do terminate fatally. The autopsy material in these cases is scanty, but occasionally the patients die with symptoms of acute cardiac failure and pneumonitis.[7]

6. Naide, M.; Sayen, A., and Comroe, B. I.: Characteristic Vascular Pattern in Patients with Rheumatoid Arthritis, Arch. Int. Med. **76**:139 (Sept.) 1945.

7. Rosenberg, E. F.; Baggenstoss, A. H., and Hench, P. S.: The Cause of Death in Thirty Cases of Rheumatoid Arthritis, Ann. Int. Med. **19**:114 1943.

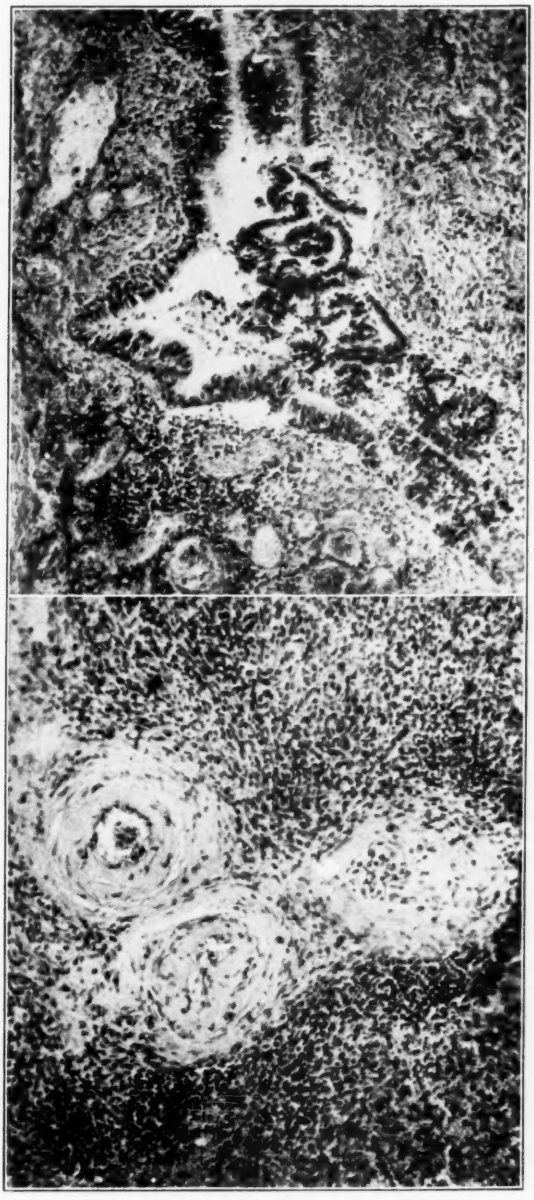

Fig. 4.—Rheumatoid arthritis. Top, section of the lung showing diffuse atelectasis with pneumonitis, perivascular round cell infiltration and desquamation of the epitheliums of the bronchi with exudate; × 140, hematoxylin and eosin. Bottom, section of the spleen showing prominent thickening of the blood vessel walls with hyaline and collagenous degeneration; × 140, hematoxylin and eosin.

At autopsy the lungs show, besides partial collapse of alveoli, unusual hyaline-like thickening of the alveolar walls and infiltration with mononuclear cells. The pleura is usually thickened and shows fibrinoid degeneration.[8] The pericardium also shows similar thickening due to fibroblastic proliferation and collagen deposition. There are adhesions of the layers of the pericardium, with complete obliteration of the sac. The myocardium shows slight to moderate degenerative changes, more notable in the subepicardial region. There is often perivascular

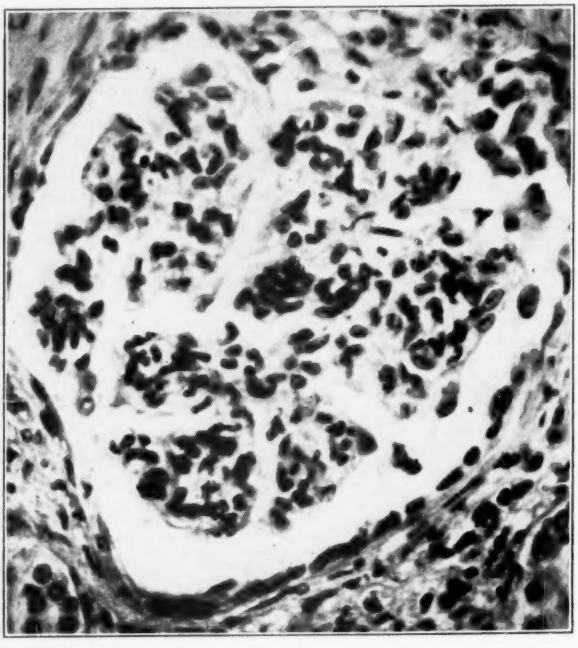

Fig. 5.—Rheumatoid arthritis. Section of the kidney showing pronounced thickening of the basement membranes of the tufts with fusion and proliferation of the endothelial cells; × 950, hematoxylin and eosin.

infiltration by large mononuclear cells simulating the Aschoff bodies that are seen in rheumatic fever. The kidneys show moderate to advanced degenerative changes involving the glomerular tufts and

8. Friedberg, C. K.; Gross, L., and Wallach, K.: Nonbacterial Thrombotic Endarteritis Associated with Prolonged Fever, Arthritis, Inflammation of the Serous Membranes, and Widespread Vascular Lesions, Arch. Int. Med. **58**:662 (Oct.) 1936.

peritubular arterioles. There is perivascular round cell infiltration with thickening of the blood vessel walls due to collagen deposit, the usual panarteriolitis.

Clinically again, the diffuse symptoms and the urinary findings can be explained only by vascular lesions involving all organs. This is well corroborated by the postmortem changes. The changes which we observed in these cases are those of chronic lesions due to repeatedly intense insults on the vascular system. The perivascular infiltration seen in less severe cases is the response to the mild stimulus. One must imagine this multiplied manyfold and the stimulus increased in intensity. The vessels respond to each episode with healing fibrinous and collagen deposition, until finally the terminal pathologic picture is reached.

Again, the relation of this disease to the aging process of vessels is evident, varied only by the intensity of the exciting stimulus and the individual response.

Case 3.—*Periarteritis Nodosa.*—Mrs. L. W., a 64 year old white woman, was first seen April 12, 1936, with the chief complaint of pain in the legs of two months' duration. Pain was bilateral and cramplike in the area of the gastrocnemius. It was present only in the dependent position. No color or temperature changes in the skin were noted. Systemic review gave negative results except for "asthmatic influenza" the previous year.

Physical examination revealed an aged white woman. The blood pressure was 158 systolic and 80 diastolic. Other physical findings were normal. Popliteal and dorsalis pedes pulsations were palpable. The red blood cell count was 3,900,000 and the white blood cell count, 14,350, with 84 polymorphonuclear leukocytes and 16 lymphocytes. The urine was essentially normal.

In May the patient began to feel extremely weak and for two days had pain and numbness from the elbow to the finger tips of the right hand. Results of examination were entirely normal. Four days later, the patient was unable to walk and had sharp shooting pains in both legs. Her temperature was now 102 F. The tongue was smooth, red and painful.

On May 9, except for a temperature of 102 F., results of physical examination remained normal. Glossitis persisted, and an alteration in vibratory sense and diminution of sensation in both legs first appeared. There was also a bilateral foot drop. Pernicious anemia was suspected. On May 11, tingling and sharp shooting pain in the right arm occurred. Two days later this condition invaded the left arm. It became progressively worse until there was complete loss of mobility of the arms, with disappearance of position sense and pain and temperature sensation, and bilateral wrist drop. Temperature was 101 F. Pulse was 120 per minute. The blood pressure was 160 systolic and 90 diastolic. The tongue was red and smooth. The reflexes were diminished in the upper extremities but absent in both legs. Motor weakness was present in all the extremities, especially in the right arm. Atrophy of the small muscles of the hands was prominent. Vibratory and position sense was lost in the legs. Liver therapy was administered without improvement.

*Laboratory Findings.*—The Wassermann and Kahn reactions were negative. The spinal fluid revealed nothing of note. Gastric analysis showed hyperchlor-

hydria. There were a trace of albumin in the urine and occasional hyaline casts and white blood cells. Nonprotein nitrogen was 40 mg. per hundred cubic centimeters. No trace of heavy metals was detected in the urine. The hemoglobin concentration was 63 per cent. Red blood cells numbered 3,400,000 and white blood cells, 16,250, with 91 polymorphonuclear leukocytes and 9 lymphocytes. Reticulocytes remained at 1 per cent in spite of therapy and red blood cells were microcytic without stippling. A series of roentgenograms of the gastrointestinal tract was normal in appearance.

*Course in the Hospital.*—Throughout a three week stay in the hospital, the neurologic picture did not change in spite of administration of liver, vitamin $B_1$, hydrochloric acid, iron and transfusions. Weakness increased in severity. On May 27, the patient had a brief syncopal attack while lying in bed. This was accompanied with severe abdominal pain and dizziness. The temperature fluctuated daily from 98 to 101 F.; the pulse rate ranged from 100 to 120. The patient, unimproved, left the hospital on June 2. At home, weakness increased; the neurologic picture did not change. On June 3, persistent vomiting along with abdominal pain occurred. Aphasia supervened. She died June 6.

*Gross Autopsy Observations.*—Postmortem studies revealed severe anemia, chronic myocardial degeneration, congestion and edema of lungs, chronic mesenteric adenitis, ileitis, septic splenitis, edema of the brain, chronic perihepatitis, bilateral symmetric atrophy of the lower extremities, periarteritis nodosa involving all the parenchymatous organs, chronic myocardial degeneration, edema of the brain and chronic nephritis.

*Comment.*—This disease has been diagnosed formerly only at the postmortem table; but recently cases have been diagnosed from muscle biopsy by study of the changes in the arterioles.[1a] If there is a disease which speaks strongly for the vascular thesis in the pathogenesis of this group of diseases, then it is polyarteritis or panarteritis nodosa. Not only are the vessels throughout the body involved, but all stages of the inflammatory process may be seen in the various organs.[9] If one examines the material at autopsy carefully, one finds various phases of the inflammatory process in the vessels of the same organ. Although the name of the disease signifies the inflammation to be limited mainly to the adventitia and surrounding tissues of the arteries, one can see involvement of all the layers by inflammatory reaction.[10] It is more appropriate to use the terms "panarteritis" and "panarteriolitis." In the early phase of the disease, eosinophilic cells are present, and infiltration is more notable through the adventitia; however, it is not constant, and at this stage most of the cells may be polymorphonuclear neutrophils. The disease is insidious with many remissions and exacerbations, the vascular damage increasing progressively. The end stage of the disease is characterized by fibroblastic changes, collagenous deposits and fibrinoid degeneration.

9. Bernstein, A.: Periarteritis Nodosa Without Peripheral Nodules, Diagnosed Antemortem, Am. J. M. Sc. **190**:317, 1935.

10. Haining, R. B., and Kimball, T. S.: Polyarteritis Nodosa, Am. J. Path. **10**:399, 1934.

Clinically, the symptoms are bizarre and unpredictable, depending on the group of vessels involved and the severity of involvement. The kidney is most frequently affected and the signs are easiest to observe. The spleen, liver, mesenteric vessels, coronary vessels and cerebral vessels are all liable to injury, producing the characteristic symptoms referable to the involved organ. Peripheral nodulations along the course of the vessels are rarely seen, although there is no doubt that the vessels throughout the body are affected. Anemia is often a prominent symptom, as in this case, but has been rarely noted in the literature. It may resemble pernicious anemia or the anemia of avitaminosis. A septic course is frequent. The recurrent episodes and remissions, the bizarre and often transient symptoms and the frequency of renal lesions and anemia should be noted as fairly constant in this most inconstant of diseases.[11]

To parallel this condition with the accelerated aging process is more difficult. The vessels are often in a stage of acute or subacute inflammation. Others, however, are seen to be scarred and hyalinized. The stage seen depends, of course, on the intensity of the stimulus and the number of remissions to allow for healing and fibrosis. In many cases of polyarteritis, the stimulus is so intense that death occurs while the involved vessels are still in a stage of acute inflammation; however, if one searches carefully, evidence of scarring in some of the vessels will always be seen.

CASE 4.—*Generalized Visceral Thromboangiitis Obliterans.*—A. S., a 21 year old white man of Jewish extraction, was first admitted to the hospital in 1930 with bronchopneumonia. At the time he complained of pain and paresthesias of the right leg. He recovered and was discharged. Five months later he was readmitted, complaining of swelling of the right leg and intermittent claudication of both legs. He improved on conservative therapy and was discharged. Three months later, in August, his complaints were of petechiae of both extremities and painful ulcers on both legs. He recovered again and was discharged.

In January 1932, he was admitted with a history of recurrent attacks of abdominal cramps localizing in the right lower quadrant. The petechiae persisted. The patient improved without surgical treatment. Bleeding and coagulation times and platelet counts were normal on all occasions. Three months later he was readmitted with the same complaint. Appendectomy was performed, and a normal appendix was removed. The patient was studied for purpura at another clinic, where results of all tests were within normal limits. Tonsillectomy and adenoidectomy were performed and he improved.

In September 1937, the patient was seen again, the chief complaint being an infection of the second toe of the left foot following trauma. Osteomyelitis necessi-

11. Rich, A. R.: Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarteritis Nodosa: Another Case Associated with a Sulfonamide Reaction, Bull. Johns Hopkins Hosp. **71**:123, 1942. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration that Periarteritis Nodosa Is a Manifestation of Hypersensitivity, ibid. **72**:65, 1943.

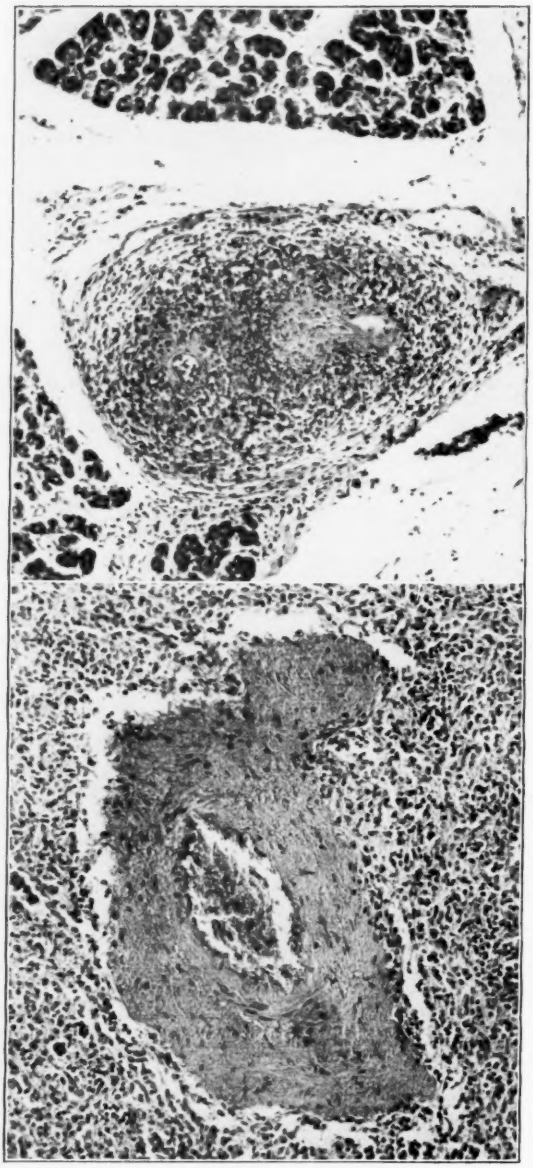

Fig. 6.—Periarteritis nodosa. Top, section of the pancreas involving two arterioles with extensive perivascular leukocytic infiltration and also hyaline and collagenous degeneration of the vascular walls; × 140, hematoxylin and eosin. Bottom, section of the spleen showing pronounced thickening of all the layers with hyaline and collagenous degeneration; × 140, hematoxylin and eosin.

tated amputation. His recovery was uneventful. Neither dorsalis pedis was palpable at this time. No purpura was noted. On Sept. 8, 1938, the patient was readmitted with gangrene of the right foot and severe precordial pain associated with fever, leukocytosis, and rapid sedimentation rate. After two weeks of conservative therapy for the cardiac condition, an amputation was performed of the right leg above the knee. Recovery was uneventful.

Subsequently, the patient had the third toe of the left foot amputated and numerous ulcers of the left leg developed.

On Oct. 22, 1942, he was again admitted with the chief complaint of severe recurrent abdominal cramps and signs of intestinal obstruction. The abdomen was rigid. This was accompanied with severe pain in the left leg and clinical signs of shock. The patient was treated conservatively and recovered. An electrocardiogram showed "myocardial damage." From local absorption of sulfonamide powder applied to the ulcers of the left leg the sulfonamide level in the blood was 3.7 mg. per hundred cubic centimeters.

On Jan. 26, 1943, the patient was readmitted with severe abdominal pain. This had begun three days prior to admission. It was intensified following the making of a series of roentgenograms of the gastrointestinal tract. The pain was continuous and persistent. The abdomen was distended with generalized exquisite tenderness, muscular rigidity and absence of peristalsis. Clinical shock was obvious. A laparotomy was performed, and a partially gangrenous portion of the ileum was observed and resected. The course of the patient's illness was downhill following operation, and he died two days later.

*Observations at Autopsy.*—Autopsy revealed massive thrombosis of mesenteric, portal and splenic veins with gangrene of the small intestine and part of the large bowel, recent laparotomy, with resection of gangrenous loop of bowel and ileostomy, amputation of the right leg, extensive healed ulcers of the left leg, old myocardial infarctions involving the wall of the left ventricle and septum and bilateral congestion and edema of the lungs.

*Comment.*—This disease has been carefully studied for the past three decades as to etiologic factors, pathogenesis and pathologic damage in the vessels that are involved. In the earlier studies, attention was directed to peripheral vessels. That the vessels are primarily involved in this disease is almost universally accepted. Sections from these blood vessel walls showed extensive inflammatory reaction generally involving all the layers and especially the intima. The thrombotic changes in the lumens were a manifestation of inflammation of the intima. At that time, attention was focused mainly on the arteries, but it is now known that in a majority of cases the veins are also involved.[12] Little was known about the vessels supplying the internal organs because of lack of postmortem studies. Within the last two decades, postmortem studies both in this country and abroad have revealed common involvement of the internal vessels.[13] Cases have

12. Edwards, E. A., and Edwards, J. E.: The Venous Valves in Thromboangiitis Obliterans, Arch. Path. **35**:242 (Feb.) 1943.

13. Housner, E., and Allen, E. V.: Generalized Arterial Involvement in Thromboangiitis Obliterans Including Report of a Case of Thrombo-Angiitis Obliterans of Pulmonary Artery, Proc. Staff Meet., Mayo Clin. **15**:7, 1940.

been reported in which cerebral, coronary,[14] mesenteric,[15] pulmonary, ophthalmic and renal vessels have been involved. In some cases only one organ was involved; in others there was multiple involvement. In general, most of the vessels of both the arterial and the venous systems were involved. In the later stages, after fibrosis and hyalinization, one cannot differentiate the changes in the vessel wall from those found in advanced arteriosclerosis.[16]

The cardiac changes in thromboangiitis obliterans differ from those in arteriosclerotic or hypertensive heart disease in that they are found in much younger persons and may be present as early as the age of 20 years. Cardiac lesions depend mostly on the stage of inflammation. If it is an early stage, cellular infiltration, mostly mononuclear and occasionally eosinophilic, is more prominent. All the layers may be involved in this stage, and early thrombotic changes may be observed. It is curious to note that the main coronary arteries are seldom involved, but that generally only the smaller arteries show changes. In the later stages of the disease, the cellular infiltration is replaced by fibroblasts and collagenous tissue, and the myocardium shows patchy fibrosis replacing the myocardial cells. Microscopic study further reveals the end result of the inflammatory and degenerative process, with cicatricial changes throughout the myocardium. When renal vessels are involved, the picture is that of interstitial nephritis. The changes in the vessels of the extremities are generally in the large or the medium-sized vessels and result in organization of the thrombus with fibroblasts and collagen deposited throughout the layers of the vessel wall. We should like to emphasize again that the veins are involved in the pathologic process.

Notoriously, thromboangiitis obliterans is a well defined clinical entity. The signs incident to the peripheral vascular involvement are obvious. It is only recently that the diffuse vascular implications, with their concomitant damage to viscera, have been recognized. This point is not well known to clinicians and is worthy of emphasis. Needless to say, the vascular damage precedes and is responsible for

14. Sclar, M.: Coronary Thrombosis: Relationship to Thromboangiitis Obliterans, New York State J. Med. **37**:1638, 1937. Eppinger, E. C.: Thrombo-Angiitis Obliterans: A Case with Extensive Distribution of the Vascular Lesions Including the Coronary Arteries, in Medical Papers Dedicated to Henry Asbury Christian, Physician and Teacher, in Honor of His Sixtieth Birthday, Baltimore, Waverly Press, Inc., 1936, p. 157.

15. Averbuck, S. H., and Silbert, S.: Thrombo-Angiitis Obliterans—the Cause of Death, Arch. Int. Med. **54**:436 (Sept.) 1934. Cohen, S. S., and Brown, M. E.: Thrombo-Angiitis Obliterans with Special Reference to Its Abdominal Manifestation, New England J. Med. **214**:1275, 1936.

16. Saphir, O.: Thrombo-Angiitis Obliterans of the Coronary Arteries and Its Relation to Arteriosclerosis, Am. Heart J. **12**:521, 1936.

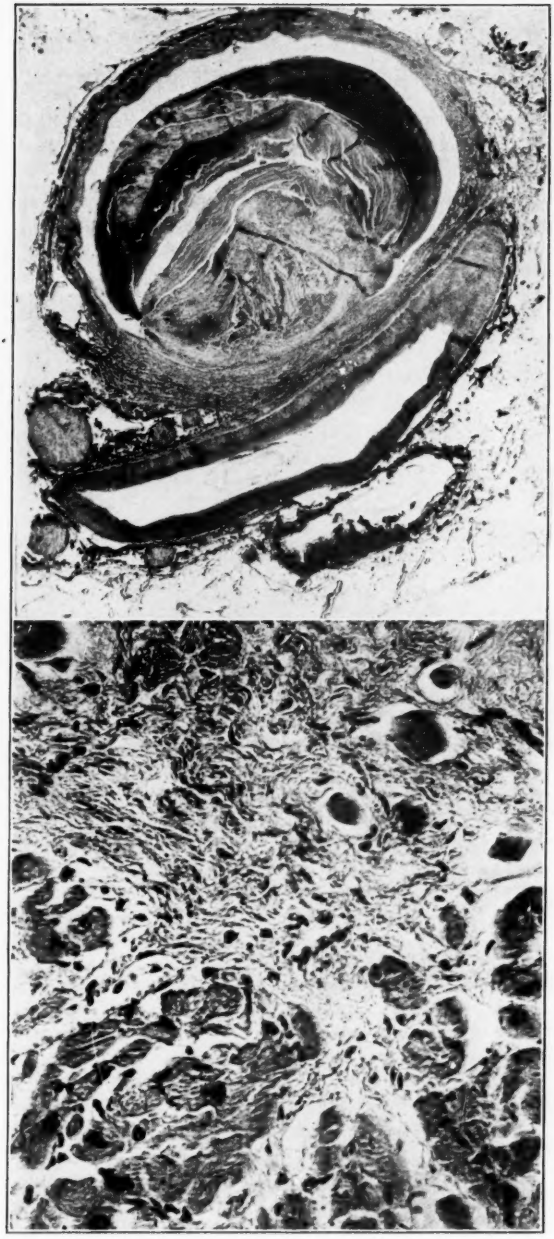

Fig. 7.—Thromboangiitis obliterans. Upper part, section of the mesenteric vein showing thrombosis with partial organization and canalization; × 20; hematoxylin and eosin. Lower part, section of the heart showing pronounced fibrosis replacing the degenerated myocardial cells caused by old infarction; × 800, hematoxylin and eosin.

the visceral or peripheral symptoms. In the case presented, the peculiar purpuric lesions may be interpreted as evidence of diffuse vascular involvement.

The analogy to the aging process is evident only when the vessel affected by healed thromboangiitis obliterans, with fibrosis, hyalinization and compromise of the lumen is compared with the usual arterio-

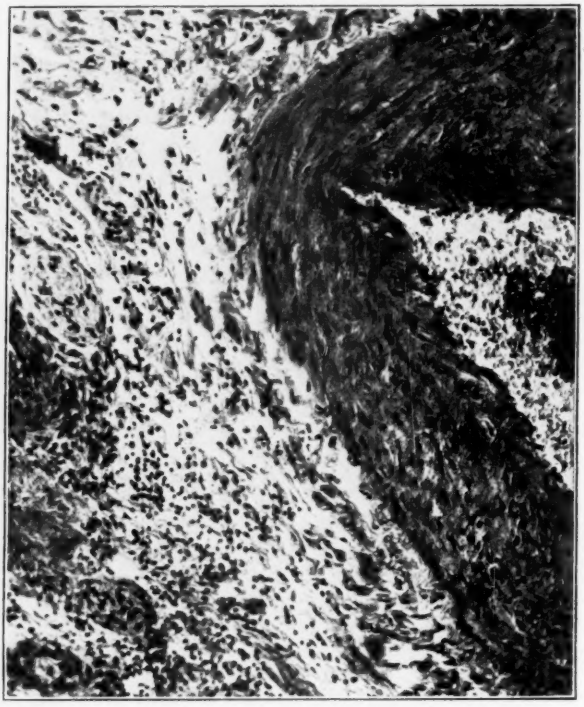

Fig. 8.—Thromboangiitis obliterans. Section of a large blood vessel with inflammatory changes of the vasa vasorum; × 140, hematoxylin and eosin.

sclerotic process. The intensity of the stimulus in thromboangiitis obliterans is usually so severe as to necessitate amputation or death in the acute or subacute stage prior to the end stage of healing.

Case 5.—*Scleroderma.*—Mrs. E. M., a 59 year old white woman, was admitted to the hospital on April 9, 1944, with the chief complaint of swelling of the hands and inability to move the fingers. The onset of the present illness was about two years prior to admission. It began with intermittent swelling of the hands. In addition, the patient complained of arthritic pains in the knees,

shoulders and ankles. Swelling of the hands persisted. The previous year it was noted that the skin was becoming harder and firmer and limited in motion. Transient swellings of the feet developed, and the skin became hardened in this area. It was noted that when the hands were exposed to cold, a bluish discoloration quickly appeared. This was followed by paresthesias. The blue discoloration persisted for several hours and disappeared only with warmth. Hardening of the fingers and skin above the wrists had progressed. There were transient swellings of the feet and ankles. Since December 1943, transient facial edema occurred. In addition, the patient complained of weakness, anorexia and a loss in weight of more than 15 pounds (6.8 Kg.) in the past six months. Dyspnea occurred recently, and the patient could not walk more than a few steps without incurring serious shortness of breath. There was inability to open her mouth completely in the past two months. This was accompanied by a "drawing" sensation in the neck. Numerous episodes of vomiting at mealtime had occurred in recent weeks, and the patient experienced vague, colicky pains after eating.

*Physical Examination.*—Examination revealed an aged, white woman of dark complexion lying quietly in bed in no acute distress. The head and neck were essentially normal, except that the skin about the neck and mouth was somewhat thickened, which impeded the patient's ability to open her mouth completely. The chest showed some dulness to percussion bilaterally, both posteriorly and inferiorly. A few crackling rales were present at these areas. The blood pressure was 140 systolic and 85 diastolic. The pulse was 100 per minute and regular. Heart sounds were of good quality and intensity. There was reduplication of the first apical sound; the second apical sound was greater than the second pulmonic sound. The abdomen showed no abnormality. There was slight, generalized abdominal tenderness. The liver and spleen were not palpable. The fingers were swollen and hard. The skin was taut over these areas. The digits were cold and pale, the pallor and coldness extending into the skin of the lower forearm. The fingers could not be flexed. The skin over the feet and ankles was somewhat thickened, and the change extended to the lateral aspect of the right knee. There were scaling of the skin and slight pitting edema of both feet in the pretibial area. The skin covering the feet was not as hard as that over the hands.

*Laboratory Findings.*—Urinalysis gave a 3 plus and a 2 plus reaction for albumin. The reaction for sugar was negative. There were 3 to 5 red blood cells and an occasional white blood cell with many granular casts. Hemoglobin concentration was 53 per cent; 3,400,000 red blood cells and 15,200 white blood cells were present, with 91 polymorphonuclear leukocytes and 9 lymphocytes. Blood sugar measured 78 mg., nonprotein nitrogen 240 mg., creatinine 11.4 mg., serum protein 4.99 Gm., serum albumin 2.69 Gm. and globulin 2.30 Gm., per hundred cubic centimeters. The test with phenolsulfonphthalein, after injection of the dye, showed no excretion of urine for two hours.

*Course in the Hospital.*—The patient's temperature during her stay in the hospital was normal. She had some insomnia and showed a progressive decline with increasing weakness, anorexia and generalized abdominal distress. On April 16 she suddenly became dyspneic and nonresponsive and died within half an hour.

*Autopsy Observations.*—Postmortem examination showed diffuse scleroderma, pericardial effusion, bilateral hydrothorax, chronic myocardial degeneration, hepatomegaly, interstitial nephritis, atrophic oophoritis, generalized arteriosclerosis,

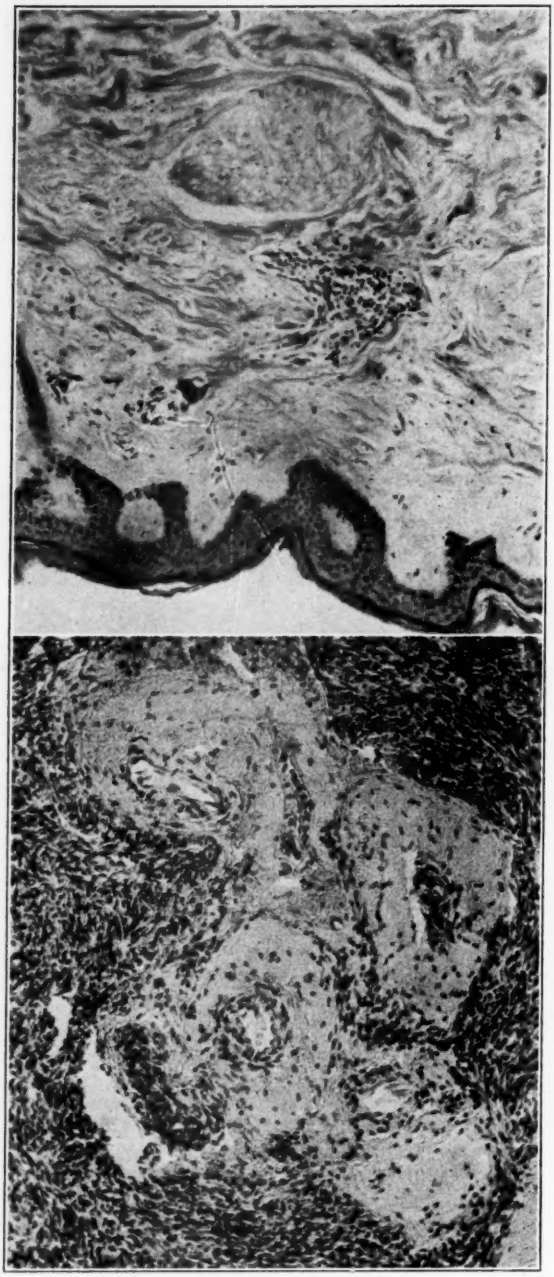

Fig. 9.—Scleroderma. Top, section of the skin showing moderate cornification of the epidermis, diffuse collagen deposit in the cutis vera and islands of perivascular round cell infiltration; × 140, hematoxylin and eosin. Bottom, section of the spleen showing collagen deposit of the media and adventitia and also narrowing of the lumens; × 140, hematoxylin and eosin.

including the coronary arteries, chronic passive congestion of the liver, arteriosclerotic contracted kidneys, hypoplasia of thyroid and ovaries, sclerosis of the skin with advanced vascular degeneration and edema and congestion of the lungs.

*Comment.*—The clinical manifestations of this disease are out of proportion to the pathologic changes at autopsy unless there is some terminal complication. From the gross and microscopic changes alone, one often cannot find the actual cause of death. The commonest observations in this malady are extreme proliferation of fibroconnective tissue and fibrinoid degeneration.[17] Sections of the skin and subcutaneous tissue show complete replacement of the areolar structures. The blood vessels also show fibrinoid degeneration of the walls with narrowing of the lumens.[18] At the terminal stage of the disease, little, if any, cellular infiltration is noted.

The pathologic changes of the internal organs are not constant or prominent. Some cases may show advanced myocardial degeneration due to damage to the coronary arteries comparable to that seen with coronary arteriosclerosis.[19] Others show changes in the kidney, especially in the glomeruli, with hyaline degeneration and collagenous deposits in the walls of the capillary tufts.[20] If this damage is extreme, the patient may die from uremia.

Several authors emphasized the sclerosis of the connective tissue of the esophagus which produces dysphagia as a clinical symptom. Clinically, the renal lesions are again prominent and easily recognized. Although the cutaneous lesions are most evident, the involvement of the viscera is becoming more widely recognized and is of more import in the ultimate course of the patient's illness. The lesions in the heart, kidney and other parenchymatous organs, where mesenchymatous tissue is a dominant part of the tissue structure, as well as the site and nature of the lesions, i. e., primarily involvement of vessels with subsequent degeneration, necrosis and fibrosis of the tissue supplied distally, again lend credence to the thesis of a diffuse vascular involvement. The fibroconnective tissue proliferation and "fibrinoid" degeneration are not incompatible with a primary vascular involvement. The simple keloid is an excellent example of the tremendous overgrowth which the poorly differentiated and unspecialized cells—the fibroblasts—may assume when subjected to the stimulus of surgical treatment or trauma.

17. Masugi, M., and Yä, S.: Die diffuse Sklerodermie und ihre Gefässveränderung, Virchows Arch. f. path. Anat. **302**:39, 1938.

18. Rake, G.: Pathology and Pathogenesis of Scleroderma, Bull. Johns Hopkins Hosp. **48**:212, 1931.

19. Pollack, A. D.: Visceral and Vascular Lesions of Scleroderma, Arch. Path. **29**:859 (June) 1940.

20. Banks, M. B.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, Libman-Sachs Syndrome and Polyarteritis Nodosa? New England J. Med. **225**:12, 1941.

It is our contention that this stimulus is primarily an anoxemic one or is caused by interference with the vascular supply. The stimulus incurring vascular damage in scleroderma is a weak but progressive one as can be gathered from the history of the case presented, i. e., symptoms of transient swellings and arthritic pains of two years' duration prior to the onset of clinically evident scleroderma. The vessels are finally sclerosed and hyalinized to the point where the tissues which they supply are never adequately oxygenated or nourished,

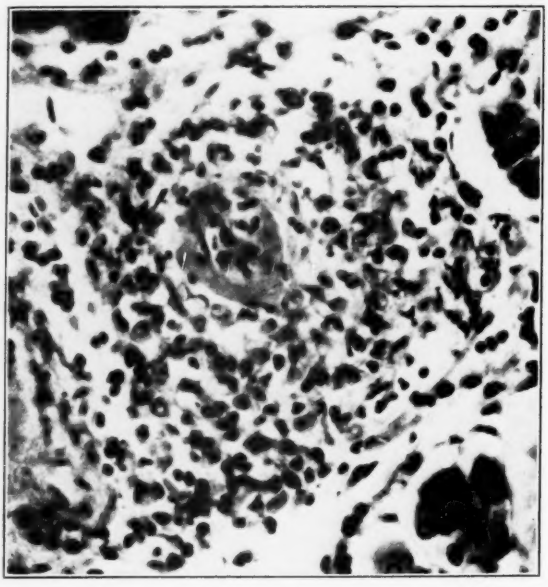

Fig. 10.—Scleroderma. Section of the kidney showing arteriole with prominent inflammatory reaction involving all the layers extending into perivascular area; × 900, hematoxylin and eosin.

but at this time pathologic examination no longer shows cellular infiltration perivascularly because the terminal scarring phase is already in progress. Diffuse atrophy further adds to the increase in sclerosis and hyalinization of the tissue, once clinical symptoms have appeared. One must not be hasty in drawing inferences as to the pathogenesis of this disease from the scarred and terminal result. Rather one should realize that this process is occurring elsewhere in the viscera where it is at an earlier phase. This will help one to implicate the vessel as the original site of ravage by this disease process.

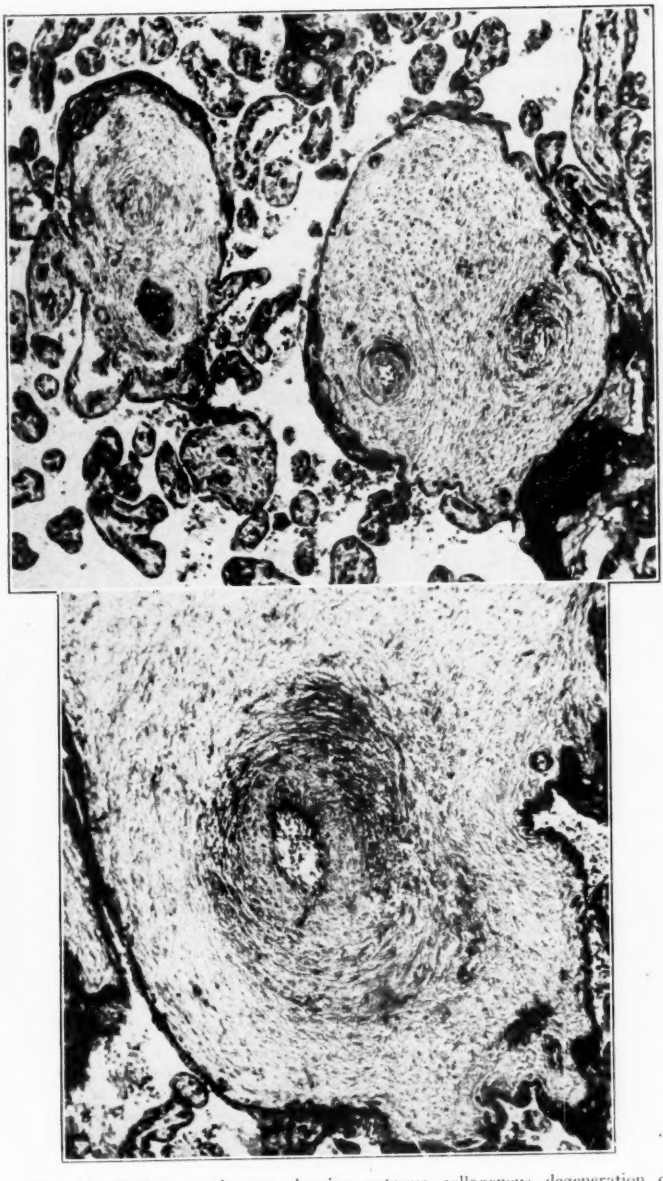

Fig. 11.—Full term placenta showing extreme collagenous degeneration of the arterioles involving all the layers and the perivascular area; × 140, trichrome.

The similarity between the vessels in chronic scleroderma and those in arteriosclerosis of old age is striking. The logical conclusion, then, is that this is but the terminal stage of healing of lesions in the vascular system due to any noxious agents, be they the trivial but accumulating ones of arteriosclerosis or the relatively more intense and rapidly progressive ones of scleroderma.

## COMMENT

Routine studies of histologic preparations taken from placentas at various stages of development will show definite aging of blood vessels. This is particularly pronounced as the placenta nears full term. There is advanced "fibrinoid" degeneration of the walls of the blood vessels, with fibroblastic changes of the media and intima. These vascular changes are comparable to the degenerative arteriosclerotic and atherosclerotic changes found in elderly people. It is obvious from studies of these slides that in the natural processes of wear and tear of tissue and in repair, fibroblastic proliferation and deposition of collagenous substance are more extensive in persons above middle age than in those who are younger.

In routine studies of sections of appendixes one can observe that incidentally appendectomized specimens show gradual replacement of lymphoid tissue by fibrinous connective and adipose tissue. This is not true in appendixes that are acutely inflamed or in those in which inflammation has subsided. Eosinophils are also often seen infiltrating the mucosa and submucosa. Careful investigation of the clinical histories of these patients showed that none of them apparently had any symptom pertaining to inflammation of the appendix. We should also like to mention that none of these appendixes contained parasites nor had there been any history of parasitic infestation.

It is a well known observation that the medium-sized arteries and arterioles of the uterus and ovaries show advanced hyalinization of the media and intima. These changes are out of proportion to the age of the person from whom the organs have been removed. Furthermore, these advanced vascular changes are unrelated to the condition of the vessels of the remainder of the body.

These observations further emphasize that the degenerative process is not always uniform throughout the body; it is certainly not uniform among various persons. As mentioned previously, the placental vessels show as much degenerative change as one expects to see in an aged person who died a natural death. We are not attempting to give the exact etiologic origin of these changes, but we do endeavor to correlate the pathogenesis of various conditions similar in that the pathologic change is predominantly in medium-sized vessels. It is our opinion that these diseases have no single etiologic factor but rather a multiplicity of causative agents, toxic in character and working together.

These, coupled with the peculiarity of reaction of the affected person, will add up to the particular type of response of his vascular tree, thus creating the specific clinical picture.

The fundamental pathology of blood vessel changes has a direct relation to the type of exciting cause, to the intensity, to the consistency of the noxious agent or agents and to the response of the individual person. If the exciting cause is mild, the reaction consists of intercellular infiltration, chiefly of eosinophils or mononuclear cells. This reaction is reversible with no permanent tissue damage resulting. The practicing physician often disregards this acute and early phase characterized by fever, myalgia, arthralgia and malaise as a "cold," an infection of the upper respiratory tract, or influenza.

If the toxic agent is moderate, in addition to the aforementioned reactions, the cellular infiltration is augmented with approximately 50 per cent of polymorphonuclear cells and many eosinophils. In addition, there are varying degrees of intracellular and extracellular edema. This type of injury to the blood vessel wall is partially reversible, with some permanent damage to the vessel wall on healing, such as fibrinoid degeneration, thickening of the wall with slight fibroblastic changes and moderate narrowing of the lumens. Varying stages of this degenerative process can be observed in the same patient.

When the toxic agent is severe, there is, in addition to the changes of the first two phases, necrosis of the intima, the media and, occasionally, the adventitia. The infiltrating cells are usually neutrophilic polymorphonuclear cells. Severe edema is present intracellularly and extracellularly. Besides fragmentation, there is granular degeneration of the endothelial and smooth muscle cells, and also proliferation of the fibroblasts of the adventitia. Intravascular thrombosis due to intimal necrosis is not uncommon.

The fourth stage is the end result of the healing process and consists of hyalinization, fibrosis and deposit of collagenous substance that replaces damaged tissue. There may be a few remnants of leukocytes, usually monocytic in type. This process is slow and insidious. With the advent of acute exacerbations, damage increases slowly. Healing occurs to varying degrees with each remission. This continues until irreparable damage has been done.

The parenchymatous organs are damaged in proportion to the circulatory disturbance caused by vascular changes. A well established observation shows that chronic anoxia produces degenerative changes, followed by fibrosis and healing.

Until recently, we had only postmortem specimens to study. In the cases reported here we have seen varying stages of the reparative process. This again depends on the individual person, the exciting stimulus, the duration of its action and the response in healing of the subject.

Since the relatively recent advent of biopsy studies on living patients, we have a more complete picture of the process. We now realize that there is an acute, inflammatory phase which precedes the healing process, allowing us a more intelligent interpretation of the chronic lesions observed so late in the course of the disease.

The concept of "accelerated aging" of vessels is then in great measure dependent on noxious agents, according to type, intensity and individuality of response in healing.

## SUMMARY AND CONCLUSION

Reports of 5 interesting cases, with clinical data, are reviewed and correlated. From postmortem studies, both anatomic and microscopic, we conclude that no specific diagnosis could be made pathologically without the clinical data.

The parenchymatous damage is proportional to the vascular changes. Lesions occur most constantly in the following organs in order of frequency: (*a*) kidneys, (*b*) serous membranes, (*c*) myocardium, (*d*) lung, (*e*) spleen, (*f*) liver and (*g*) skin. The organ primarily affected in the so-called diffuse vascular or collagenous disease is the small arterioles and capillaries and indirectly the larger vessels by way of the vasa vasorum. The chronic anoxemia thus produced caused degenerative changes in the surrounding collagenous tissue.

The term "fibrinoid" degeneration and collagenous disease is descriptive only as to the end result of the pathologic process.

This "accelerated aging" of vessels depends on the type, intensity and constancy of noxious agents and the individual healing response.

The photomicrographs were by Mr. Albert Levin, F.B.P.A.

Fifth Avenue at Darraugh.

# REACTION OF THE BODY TO POLIOMYELITIS AND THE RECOVERY PROCESS

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A YEAR and a half ago, while engaged in the study of clinical neurosurgery and neurology, I personally had a severe attack of poliomyelitis. Previously, I had also spent two years in neurophysiologic research, studying botulinus toxin, which causes a paralysis not unlike that of poliomyelitis.[1] Therefore, I have followed my case with considerable interest, and I hope that the present discussion will make this experience of value to the entire medical profession.

## I. FUNDAMENTAL CONCEPTS OF THE DISEASE

*A. Virus Etiology.*—It is relatively certain that poliomyelitis is caused by a small virus which is hardy, resists many of the disinfectants, can live for long periods at low temperatures, exists abundantly in sewage during times of epidemics and is widespread among the populace.[2] Independent observers have shown by electron microscopy that the virus is approximately 25 microns in size, with either a spherical or a slightly asymmetric body.[3] A strain of the virus has been isolated in a pure form, 1 Gm. of which will infect and kill approximately one billion mice.[4] It is obvious, therefore, from the

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1. (*a*) Guyton, A. C., and MacDonald, M. A.: Physiology of Botulinus Toxin, Arch. Neurol. & Psychiat. **57**:578-592 (May) 1947. (*b*) Guyton, A. C.: A Versatile Square Wave Nerve Stimulator, Rev. Scient. Instruments **17**:553-556 (Dec.) 1946.

2. (*a*) Schultz, E. W.: Chemical Agents in the Prevention and Treatment of Experimental Poliomyelitis, Am. J. Pub. Health **30**:175-179 (Feb.) 1940. (*b*) Melnick, J. L.: Poliomyelitis Virus in Urban Sewage in Epidemic and Non-Epidemic Times, Am. J. Hyg. **45**:240-253 (March) 1947.

3. (*a*) Jungeblut, C. W., and Bourdillon, J.: Electronmicrography of Murine Poliomyelitis Virus Preparations, J. A. M. A. **123**:399-402 (Oct. 16) 1943. (*b*) Loring, H. S.; Marton, L., and Schwerdt, C. E.: Electron Microscopy of Purified Lansing Virus, Proc. Soc. Exper. Biol. & Med. **62**:291-292 (June) 1946.

4. Loring, H. S., and Schwerdt, C. E.: (*a*) Studies on the Purification of Poliomyelitis Virus, J. Exper. Med. **75**:395-406 (April) 1942; (*b*) Isolation of a Macromolecular Constituent with Properties of the Lansing Strain of Poliomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **62**:289-291 (June) 1946.

nature of the virus, that it is difficult to attack. Sterilization of air, water and food supplies as well as treatment of the actual infection is yet beyond our medical ability.

The incubation period is commonly stated to be five to thirty-five days, but in mice the infection has been known to occur as early as twenty-four hours and as late as ninety-three days.[5] Because of the difficulty in studying the incubation period in man, it is impossible to state the extremes which may occur, though from data available the average is probably around two weeks.

*B. Epidemiology.*—The epidemiology of poliomyelitis is greatly complicated by the fact that many persons have gastrointestinal poliomyelitis for each one who shows neurogenic symptoms [2b]; all these persons unknowingly transmit the disease.

There are many indications that during epidemic times poliomyelitis is spread principally through the respiratory tract rather than through food supplies. Some cases, however, particularly of a sporadic nature, undoubtedly are caused by contaminated food.[6] It has been shown that epidemics usually spread in concentric circles from the point of origin rather than over widely separated areas, a fact entirely consistent with respiratory spread rather than with gastrointestinal spread. The age incidence of poliomyelitis is much lower in urban areas than in suburban areas, which situation is likewise found in other infections of the respiratory tract such as measles but is not found in food-borne infections such as typhoid.

The prevalence of poliomyelitis in the United States has greatly increased in the last few years, the cause of which we do not know, but it has been observed in many areas of the world that as sanitary conditions have become better the prevalence of poliomyelitis also has increased and relative incidence among older persons has risen. In a thirty-six year study of poliomyelitis in Panama, the incidence among the white persons was found to be two and one-half times that among the Negro population.[7] Actually, the number of young children with the disease was less among the white persons, but the incidence among older age groups greatly overcompensated for this. A reasonable explanation for the increasing prevalence of poliomyelitis and the rising incidence of the disease among older persons is that there is considerable cross

5. (*a*) Aycock, W. L., and Kessel, J.: Infectious Period of Poliomyelitis and Virus Detection, Am. J. M. Sc. **205**:454-465 (March) 1943. (*b*) Armstrong, C.: Cotton Rats and White Mice in Poliomyelitis Research, Am. J. Pub. Health **31**:228-232 (March) 1941.

6. (*a*) Anderson, G.: The Transmission of Poliomyelitis, Journal-Lancet **66**:315 (Sept.) 1946. (*b*) Aycock and Kessel.[5a]

7. Taylor, C. E.: Poliomyelitis on Isthmus of Panama, New England J. Med. **230**:790-793 (June 29) 1944.

immunization between poliomyelitis and other diseases. Therefore, as the other diseases are conquered, many of the immunizing antigens of childhood being removed, the body is left susceptible to poliomyelitis.

*C. Spread of Poliomyelitis Through the Body.*—Regardless of whether poliomyelitis enters the body through the respiratory tract or through the gastrointestinal tract, probably in all cases a preliminary infection of the lymphoid tissue in the nasopharynx and the gastrointestinal tract occurs prior to infection of the nervous system. Although it is possible for the virus to travel to the brain through the blood or lymph, in actuality it has been shown that entry to the brain usually occurs only along the axons of nerves and that the point of entry into the central nervous system depends on which nerve the virus traverses in its course from the gastrointestinal tract or nasopharynx.[8]

The idea held a few years ago that poliomyelitis enters the brain only through the olfactory nerves of the nose has been shown to be erroneous, and, indeed, pathologic material from human beings indicates that rarely does this occur. Whether or not the virus will spread from the alimentary tract to the brain depends on many factors, including immunity, virulence of the virus, fatigue of the patient, previous infection of the patient by other organisms and probably also individual susceptibility to poliomyelitis virus. It is probable that only in one case out of a hundred in which there is alimentary infection does the virus travel to the brain.

Once the poliomyelitis virus enters the nerve trunk, approximately eleven hours lapse before the virus spreads at all. After that time it travels up the nerve at the rate of approximately 2.4 mm. per hour. This explains well the reason why there is a long incubation period in poliomyelitis, depending partly on the length of the nerve which the virus must traverse.[9]

The pathway of the virus through the central nervous system has been beautifully mapped,[8] which results in the following fundamental observations: First, the virus spreads in the brain as well as in the peripheral nerves mainly, if not only, through axonal pathways rather than through lymphatic or blood channels. Second, there are many areas of the brain and spinal cord which are resistant to the infection. Third, the course which the virus takes through the brain is dependent on the point of entry and on the axonal pathways which lead from this point. When the axonal pathways lead to resistant areas, the infection stops at these points and travels no farther. Fourth, in most cases of

8. Howe, H. A., and Bodian, D.: Neural Mechanisms in Poliomyelitis, New York, The Commonwealth Fund, 1942.

9. Bodian, D., and Howe, H. A.: The Rate of Progression of Poliomyelitis Virus in Nerves, Bull. Johns Hopkins Hosp. **69**:79-85 (Aug.) 1941.

poliomyelitis the infection is not stopped until it has spread to all susceptible areas of the brain and spinal cord. Fifth, the only areas of the central nervous system which are destroyed sufficiently to cause permanent symptoms usually are the anterior horns of the cord. This produces the well known paralysis. Sixth, axonal spread of the virus is somewhat faster through the central nervous system than through peripheral nerves, which explains the rapidity with which symptoms develop.

Patients with poliomyelitis suffer markedly different involvements of the nervous system and different patterns of paralysis for several reasons: First, the more virulent the virus the farther it is likely to spread, as has been shown many times in epidemics and experimental infections. Second, the susceptibility of persons is different, which depends on fatigue, local neuronal immunity, humoral immunity and individual idiosyncrasies. Local immunity of the neuronal cells may have been acquired from a previous neurogenic attack of poliomyelitis even though the patient did not realize that he had had the disease.[10] Also, local immunity may develop rapidly in the acute attack of poliomyelitis, preventing the infection from traversing the same area several times and preventing, therefore, excessive damage. Humoral immunity, as distinguished from local immunity, may exist in the form of antibodies in the blood stream and may have been acquired from a previous poliomyelitis infection not necessarily of the central nervous system but simply of the gastrointestinal tract; it is well known that specific antibodies do result from such an attack. Also extensive edema and leukocytic infiltration occur, both of which may be of importance in limiting spread of virus within any particular area.

Certain muscles of the body, such as the deltoid and the anterior tibial muscles, appear to be more susceptible to paralysis than are other muscles. The virus, in spreading through the spinal cord, attacks the dorsomedial nuclei of the anterior horns before advancing to the ventrolateral nuclei, and often the infection is stopped before this final advance. Because muscle representation in the anterior horns is in the form of longitudinal layers of neuronal cells rather than lateral, segmental layers, the greater attack rate on the dorsomedial nuclei possibly explains the greater susceptibility of some muscles to paralysis.[11]

*D. Extent of Pathologic Process.*—The poliomyelitis virus grows only in areas of the brain which have a plentiful supply of neurons and will not grow in areas of only glial cells. For this reason the destructive

10. Howe, H. A., and Bodian, D.: Second Attacks of Poliomyelitis: An Experimental Study, J. Exper. Med. **74**:145-165 (Aug.) 1941.

11. Elliott, H. C.: Studies on the Motor Cells of the Spinal Cord: V. Poliomyelitis Lesions in the Spinal Motor Nuclei in Acute Cases, Am. J. Path. **23**:313-325 (March) 1947.

process within the neurons is the primary process in poliomyelitis, whereas the infiltrative and edematous processes among the glial cells is entirely secondary.[12]

Neuronal damage occurs throughout the central nervous system, but in some specific areas it occurs much more frequently and much more severely than in others. Among the cortical nuclei the motor cortex is relatively susceptible to poliomyelitis whereas most other areas of the cortex are extremely resistant. In the brain stem the most susceptible nuclei are those in the cerebellar roof, the vestibular nuclei, and the reticular formation of the medulla.[13]

In the spinal cord the most pronounced destruction of neurons is found in the anterior horns, but there is also some relatively insignificant destruction of cells in the posterior and intermediate horns. It has been reported that the internuncial cells are in some instances markedly affected by poliomyelitis virus,[14] but many other observers have failed to note this. It has been pointed out that if the internuncial cells of any particular area are killed the anterior horn cells of the same area are also invariably destroyed.[13a] In this case the paralytic symptoms are those of flaccidity due to the loss of anterior horn cells rather than a spastic type of paralysis due to loss of internuncial cells.

Neuronal destruction is not limited to the central nervous system, for damage also occurs in the posterior root ganglions of sensory nerves and, rarely, in the ganglions of the sympathetic chain.[15]

The pathologic changes in nerves are those of any lesion of the peripheral motor neurons, beginning with wallerian degeneration of the motor nerve axons, which subsequently disappear completely within a month or more, leaving the nerve sheath itself intact. The muscle then undergoes the usual atrophy of denervation with pyknotic loss of cross striations and increase of longitudinal markings.[16] Over a period of months the muscle then undergoes fatty degeneration with or without fibrotic invasion.

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12. Bodian, D., and Howe, H. A.: Neurotropism and the Genesis of Cerebral Lesions in Poliomyelitis: An Experimental Study, Bull. Johns Hopkins Hosp. **68**:58-79 (Jan.) 1941.

13. (*a*) Bodian, D.: Poliomyelitis: Neuropathologic Observations in Relation to Motor Symptoms, J. A. M. A. **134**:1148-1154 (Aug. 2) 1947. (*b*) Sabin, A. B.: Pathology and Pathogenesis of Human Poliomyelitis, ibid. **120**:506-511 (Oct. 17) 1942.

14. Kabat, H., and Knapp, M. E.: Use of Prostigmine in the Treatment of Poliomyelitis, J. A. M. A. **122**:989-995 (Aug. 7) 1943.

15. Bodian, D., and Howe, H. A.: The Significance of Lesions in Peripheral Ganglia in Chimpanzee and in Human Poliomyelitis, J. Exper. Med. **85**:231-242 (March) 1947.

16. Dublin, W. B.; Bede, B. A., and Brown, B. A.: Pathologic Findings in Nerve and Muscle in Poliomyelitis, Am. J. Clin. Path. **14**:266-272 (May) 1944.

*E. Relation of Pathologic Process to Symptoms.*—Although in practically all cases of poliomyelitis there are lesions throughout the brain as well as in the spinal cord, there is little permanent damage except to the anterior horn cells. There may be in the acute stage of the disease, however, many other symptoms referable to lesions elsewhere than in the anterior horns.

Encephalitis, with the usual manifestations of headache, drowsiness and confusion, frequently occurs as a result of lesions in the midbrain. Yet the course of this complication is usually only a few days, and residual symptoms are rare. The encephalitis often occurs prior to paralytic symptoms, for the brain may be infected before the cord. Occasionally, however, the reverse is true, with occurrence several days to a week after the onset of spinal paralysis.

Meningitic symptoms invariably occur along with acute infection of the neurogenic parenchyma. These symptoms are not due to a direct infection of the meninges by the virus, for such does not occur. Instead, there is a sterile irritation of the meninges secondary to irritative products arising in the infected nervous tissue.[8]

Generalized bodily disturbances are present in practically every case of poliomyelitis, probably resulting from the severe lesions usually present in the brain stem. Cardiac and respiratory irregularities occur in severe cases, but much more general are the other symptoms of autonomic dysfunction which will subsequently be described in greater detail.

Lesions of the intermediate horns, the posterior horns, the peripheral sensory ganglions and the sympathetic ganglions are in general not too severe, and there is no definite evidence that any of these plays a major role in the symptomatology of poliomyelitis.[17]

In general, therefore, though many areas of the brain are infected, only the lesions of the anterior horn cells and of the brain stem cause major symptoms, producing paralysis and generalized bodily disturbances respectively.

*F. The Secondary Pathologic Changes.*—The secondary changes within the central nervous system include edema, leukocytic infiltration and, later, gliosis. It is possible but not probable that the edema could be so great that resultant ischemia might destroy cells not actually infected by the virus. The leukocytic invasion occurs after neuronal damage has taken place and might be considered a protective process attempting to destroy the poliomyelitis virus. Also, many phagocytes appear around the degenerating nerve cells, devouring these until only blank areas remain where neuronal cells were once present. After a week or more, the damaged areas are invaded by glial cells, the action of which is to restore structural characteristics as in the invasions of wounds of the skin by scar tissue.[13b]

17. (*a*) Bodian.[13a] (*b*) Bodian and Howe.[15]

## II. PATHOLOGIC PHYSIOLOGY AND SYMPTOMATOLOGY

*A. Paralysis.*—The most important symptom in poliomyelitis is undoubtedly the flaccid paralysis due to destruction of anterior horn cells. There have been instances, however, when various other mechanisms of paralysis have been suggested, such as destruction of the internuncial cells [14] and the motor cortex, but pathologic and physiologic data are not consistent with such mechanisms. If paralysis were due to destruction of internuncial cells, the motor nerve to the muscle should still be intact, and in turn the electrical excitability of the muscle should still be normal. In poliomyelitic muscles, however, the electrical excitability is greatly decreased.[18] This, as well as pathologic studies, indicates that the nerve itself is destroyed or inactivated in poliomyelitis and is sufficient to rule out destruction of internuncial cells as a major cause of the paralysis.

The paralyzed muscles of poliomyelitis show many other characteristics which appear when the nerve itself is destroyed. Fibrillation of the muscle occurs for the first few weeks and is presumably due to local irritability of the motor units located directly within the muscle. Also, beginning early in paralysis and continuing over a period of many weeks, the muscles of a patient with poliomyelitis atrophy markedly, as do muscles after nerve injury, and electrical excitation of the muscle gives the same delayed response as does excitation of the denervated muscle.[19]

In general, therefore, the paralysis of poliomyelitis is flaccid in nature and is due to actual death or inactivation of motor nerves from the spinal cord to the muscle.

*B. The Autonomic Nervous System in Poliomyelitis.*—The pathologic physiology of poliomyelitis is not concerned entirely with the paralysis of muscle itself, for in the acute disease the generalized bodily symptoms are often of more concern than the paralysis. Most of these symptoms can be ascribed to overactivity of the sympathetic nervous system.

Vasoconstriction: Among the autonomic symptoms is vasoconstriction throughout the body, which is evidenced in the acute stage by an extremely severe chilling of the entire body. Paralyzed limbs will actually be cyanotic and often edematous as a result of poor blood supply. There is reason to believe that this vasoconstriction may involve the

18. Watkins, A. L., and Brazier, M. A. B.: Studies on Muscle Innervation in Poliomyelitis and Nerve Injuries, Arch. Phys. Med. **26**:69-75 (Feb.) 1945.

19. (*a*) Solandt, D. Y.: Atrophy in Skeletal Muscle, J. A. M. A. **120**:511-513 (Oct. 17) 1942. (*b*) Solandt, D. Y.; DeLury, D. B., and Hunter, J.: Effect of Electrical Stimulation on Atrophy of Denervated Skeletal Muscle, Arch. Neurol. & Psychiat. **49**:802-807 (June) 1943.

muscles as well as the skin, though little effort has been exerted in studying this possibility.

Gastrointestinal Abnormalities: The patient early and almost invariably has an extreme lack of appetite lasting for the first two or three months, with a resultant loss of weight. This may be so severe that his body weight will fall to one-half normal. The saliva is thick and mucoid, similar to that produced during hypersympathetic activity, which causes swallowing to be exceedingly difficult. In the acute phase, constipation is extremely severe, and in many cases impaction of the bowels occurs. The constipation of poliomyelitis frequently is refractory to treatment by all common types of enemas such as those of isotonic sodium chloride solution or soap suds but will respond immediately to one containing glycerin and magnesium sulfate, which directly stimulates the peristalsis. These gastrointestinal symptoms are those of increased sympathetic activity, which is well known to cause appreciable inhibition of glandular activity and peristalsis.

Cardiac Irregularities: The blood pressure in cases of acute poliomyelitis has been known to rise considerably, to remain elevated for a month or more and to fall later to normal or even to subnormal levels. In many cases the heart rate rises 50 per cent,[20] and it remains permanently rapid in some instances. Also the patient is subject to intense emotionalism associated with rapid and powerful palpitation.

Retention of Urine: In the early days of acute poliomyelitis retention of urine is common. Pathologically, sufficient lesions within the spinal cord itself to account for this condition have not been found. Yet it is well known that emptying of the bladder is influenced by nuclei located in the pons and medulla, where severe lesions are often found.[21]

Sweating: Sweating of an extremely severe nature is another symptom of acute poliomyelitis. Even though the body be markedly chilled because of vasoconstriction, the patient often wets the entire bed. This sweating usually decreases after a few months but may persist to some extent indefinitely.

Because sweating is a parasympathetic phenomenon, one would expect other parasympathetic abnormalities. Relative degrees of priapism often occur in the male, but otherwise the parasympathetic functions, if anything, are inhibited rather than stimulated.

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20. Brown, J. R.; Baker, A. B.; Adams, J., and McQuarrie, I.: The Bulbar Form of Poliomyelitis: Diagnosis and the Correlation of Clinical with Physiologic and Pathologic Manifestations; Minnesota Poliomyelitis Research Commission, J. A. M. A. **134**:757-762 (June 28) 1947.

21. (*a*) Wang, S. C., and Ranson, S. W.: Autonomic Responses to Electrical Stimulation of the Lower Brain Stem, J. Comp. Neurol. **71**:437-455 (Dec.) 1939. (*b*) Bodian.[13a]

Locus of Lesions in the Autonomic System: Pathologically, major poliomyelitic lesions occur only in the medullary portion of the sympathetic nervous system. There have been minor lesions described in the sympathetic nuclei of the spinal cord and in the sympathetic ganglions, but these are probably too slight to produce the autonomic symptoms of poliomyelitis. On the other hand, lesions of the medulla are often extremely severe and are found probably as frequently as lesions in any other part of the brain or the spinal cord.[22]

The autonomic disturbances of poliomyelitis often occur in patients several days prior to paralysis, or, in other words, before the infection has spread from the brain to the spinal cord. For instance, the retention of urine is often the first symptom noted by the patient, which, as has been discussed previously, is probably due to lesions in the tegmentum of the pons. Likewise, other patients have as their first symptoms pain and tense, tender muscles several days prior to paralysis. Monkeys, when killed at this stage of the disease, have no lesions whatsoever in the spinal cord through the hindbrain is already markedly involved.[23]

Therefore, pathologic, physiologic, clinical and experimental evidence indicates considerable disturbance of the medullary sympathetic centers. This might explain why shortening and pain often occur in muscles which are not paralyzed.

*C. Muscle Pain and Shortening.*—Should there be vasoconstriction, symptoms of an ischemic muscle such as are found in Buerger's disease, Raynaud's disease, arteriosclerosis and immersion foot would be expected. These symptoms might be contracture, pain and tenderness of the muscle on deep palpation. Hence, there is a logical explanation for the two symptoms found in cases of poliomyelitis which have not been adequately explained previously, i.e., muscle pain and muscle shortening.

The insidious, constant pain of acute poliomyelitis is like that of muscle ischemia. One may produce similar pain in a normal person by placing a blood pressure cuff on his arm and blowing the pressure to a value sufficiently high to cut off arterial blood flow. After a few minutes the pain begins. The tenderness of the muscles in poliomyelitis is a pain of similar quality but much sharper. The muscle reacts violently to any type of pressure such as squeezing or even lying on it. Stretching the muscle induces the same sharp pain as deep pressure plus a tearing sensation. Therefore, several different types of pain might occur in poliomyelitis, all possibly due to ischemia: the steady dull pain which is truly indescribable but which may be experi-

22. (*a*) Bodian.[18a] (*b*) Sabin.[18b]

23. Bodian, D.: Experimental Evidence on the Cerebral Origin of Muscle Spasticity in Acute Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **61**:170-175 (Feb.) 1946.

enced by anyone in the fashion described, the sharp pain of deep pressure and the sharp tearing pain of the same nature which occurs on stretching the muscle.

Pain does not occur only in muscle, for some patients also have intense pains in the joints which are much the same as those of rheumatoid arthritis. These may be ascribed again to possible ischemia of the tissues.

Conditions which tend to make these pains worse are the same conditions which tend to cause further ischemia of the muscle. For instance, sitting on the glutei, with resultant ischemia of muscles, causes pain in poliomyelitic patients many months after the acute case and sometimes for years. Cold weather will cause the pain to become more severe, and massage often intensifies the pain, probably because of the increased metabolism of the muscle without increased blood supply.

On the other hand, anything that will relieve the ischemia tends also to produce relief of the pain. For instance, during periods of impaction of the bowel, with considerable palpitation and peripheral vasodilatation, all the symptoms of muscle pain are completely relieved, and this relief lasts for forty-five minutes to two hours after the impaction has been removed. Likewise, without the reason for its action being known, heat long ago was found empirically to be an effective means of relieving the pain. Heat exerts a powerful vasodilating effect which relieves the ischemia of vasospastic conditions, as is well known in Raynaud's disease. Neostigmine, a powerful vasodilator, also is effective in this regard and has therefore been recommended.[24] Even curare has a vasodilating effect, by which it possibly relieves muscle tension rather than by its effect at the myoneural junction.[25] Also, paravertebral anesthetization of the sympathetic nerves, with consequent vasodilatation, relieves the pain.[26] Unfortunately, all these pain-relieving procedures have received at various times bizarre explanations, the proponents of the theories having forgotten the common denominator of vasodilation, which alone could possibly sufficiently explain the beneficial results.

Shortening occurs in all muscles which have pain regardless of the amount of paralysis present. The same agents which relieve pain also

24. (*a*) Kabat, and Knapp.[14] (*b*) Watkins, A. L., and Brazier, M. A. B.: Observations on Muscle Spasm in Poliomyelitis, Arch. Phys. Med. **26**:325-328 (June) 1945.

25. (*a*) Ransohoff, N. S.: Treatment of Acute Anterior Poliomyelitis with Curare and Intensive Physical Therapy, Bull. New York Acad. Med. **23**:661-669 (Nov.) 1947. (*b*) Sollmann, T.: A Manual of Pharmacology, ed. 6, Philadelphia, W. B. Saunders Company, 1942, p. 419.

26. Collins, V. J.; Foster, W. L., and West, W. J.: Vasomotor Disturbances in Poliomyelitis, with Special Reference to Treatment with Paravertebral Sympathetic Block, New England J. Med. **236**:694-697 (May 8) 1947.

have a beneficial effect on the shortening process, which indicates a common vasospastic origin of the two phenomena. Indeed, it is well known that ischemic muscle conditions lead to stiffening of the muscles, with subsequent contractures.

*D. Spasm.*—Spasm is a term which has often been applied in poliomyelitis but almost always erroneously. Electromyographic studies made on patients with poliomyelitis show that in all muscles which are completely paralyzed no action currents can be detected regardless of how much the patient tries to contract the muscles.[27] Also, stimulation of these muscles by other means such as overstretching causes no action currents or only mild responses, which indicates that a completely paralyzed muscle cannot be in neurogenic spasm. Yet, these muscles undergo the same stiffening or shortening process as do other muscles. Muscles which are only partially paralyzed almost invariably are also painful on being stretched. Because of the pain, such procedure would undoubtedly elicit opposing reflexes, and obviously the electromyographic responses would be strong, but there is no reason whatsoever to consider this pain reflex as primary neurogenic spasm, for any type of pain causes the same thing.[28]

The muscle shortening in poliomyelitis has been called spasm by many physical therapists, but there is a great difference between spasm and muscle shortening. Spasm is due to the passage of an actual nerve and muscle impulse, whereas shortening of the muscle fibers is a structural change regardless of cause. As stated before, and it is worth repeating, the muscles which are completely paralyzed undergo exactly the same shortening as do muscles which are partially paralyzed, which indicates positively that this shortening is not due to a spastic condition originating from excess skeletal nervous activity.

Misunderstanding of the word spasm has greatly hindered the understanding of poliomyelitis and has actually led to misconcepts in treatment. Muscle shortening is the important pathologic change in poliomyeltis, and if neurogenic spasm does occur, it certainly is not an important cause of the shortening and probably is of little clinical importance.

*E. Atrophy of Muscles.*—Atrophy of muscles in poliomyelitis begins to occur immediately after onset of the disease, continuing rapidly for the first four months and then slowly over a period of several years.

27. Brazier, M. A. B.; Watkins, A. L., and Schwab, A. S.: Electromyographic Studies of Muscle Dysfunction in Infectious Polyneuritis and Poliomyelitis, New England J. Med. **230**:185-189 (Feb. 17) 1944.

28. (*a*) Schwartz, R. P.; Bowman, H. D., and Smith, W. K.: Significance of Muscle Spasm in Acute Stage of Infantile Paralysis Based on Action Current Records, J. A. M. A. **126**:695-702 (Nov. 11) 1944. (*b*) Watkins, A. L.; Brazier, M. A. B., and Schwab, R. S.: Concepts of Muscle Dysfunction in Poliomyelitis, Based on Electromyographic Studies, ibid. **123**:188-192 (Sept. 25) 1943.

This atrophy is due to disuse and to the lack of trophic impulses from the degenerating nerve fibers.[19a] To a certain extent the atrophy is reversible provided that the nerve to the muscle grows back. If, however, atrophy has been present for a long period, various degrees of fatty degeneration and fibrosis will have occurred, making it difficult for recovery of nerves to cause regeneration of the muscle. A muscle denervated for a period of four years usually will not recover despite regrowth of the nerve, and even after two years such recovery will be doubtful.[29] This indicates, therefore, that the nerve must resume its function early or the muscle itself will be unable to accept reinnervation.

### III. THE PROCESS OF RECOVERY

Recovery from the paralysis of poliomyelitis may be divided into three phases: first, recovery in the spinal cord; second, recovery of the peripheral nerves; and third, recovery of the muscles.

*A. Recovery in the Spinal Cord.*—Recovery in the spinal cord probably takes place within a period of two months after onset of the disease. The concentration of virus reaches a height on the day previous to the onset of paralysis and during the first day after onset. This virus then persists for approximately two weeks, during which time destruction of more neurons may possibly take place. However, most of the destruction occurs during the first three days.[30] After the first week, the recovery process begins with reduction of edema and reversal of chromatolysis in the neuronal cells which are still alive. The neuronal cells which have been killed undergo a process of neuronophagia or, in other words, phagocytosis by leukocytic cells. After approximately one month, the neuronal cells have either returned to a normal appearance or they have completely disappeared from the cord.[12a] It is difficult to believe that some neurons may remain functionally dormant for a long period because of this rapid return of normal histologic structures.

There is a belief that regrowth of internuncial cell connections to the anterior horn cells might occur for many months.[14] The length of the axons from the internuncial cells to the anterior horn cells is approximately 3 to 4 mm. Because it is known that axons in peripheral nerves grow at the rate of approximately 1 mm. per day, it is difficult to believe that internuncial cells continue to reform connections longer than two to three weeks, if this long, after the recovery process begins. Also, it

29. Cutler, C. W., Jr.: The Hand, Philadelphia, W. B. Saunders Company, 1942, p. 381.

30. Bodian, D., and Cumberland, M. C.: The Rise and Decline of Poliomyelitis Virus Levels in Infected Nervous Tissue, Am. J. Hyg. **45**:226-239 (March) 1947.

has long been known that axonal regrowth within the central nervous system is practically nonexistent.

Infiltration of the cord by glial cells occurs for the first few weeks and may continue for many months.[13b] Because these cells have much the same characteristics as fibrous cells elsewhere in the body, it is theoretically possible that fibrous compression of neuronal cells or axonal pathways might occur in the cord. This could possibly account for the many patients who lose the power to move their toes months after the acute disease or for the infrequent patients who are reputed to regain suddenly use of discrete muscles.

Therefore, insofar as proved data exist, it appears that recovery in the spinal cord takes place within the first two months or not at all. Other changes taking place in the cord after this time have been postulated but thus far remain entirely hypothetic. Such is not true of recovery of peripheral nerves and muscles, for there is much physiologic data indicating that these recovery processes may extend for several years.

*B. Recovery of the Nerves.*—The recovery of nerves may occur by two processes: first, the regrowth of axons from nerve cells which have not been killed but from which the axons have been destroyed and, second, by an arborization of axons which are still present.

Regrowth of Axons from Unkilled Nerve Cells: There is meager evidence that some axons can be destroyed by decided pressure within the nerve sheath caused by other degenerating swollen axons.[31] Obviously, this would leave healthy anterior horn cells which have no axonal connections with the muscles, in which case regrowth of the axons will take place, and recovery of muscles might occur many months after onset of the disease. Nerves grow at a speed of approximately 1 mm. per day, which means that the regrowth of the axons to areas such as the leg may take as long as five hundred to a thousand days or approximately a year and a half to three years. There is no evidence, however, that significant recovery of nerves through this process of entire axonal regeneration does occur.

Arborization of Unkilled Axons: The nature of the late recovery process indicates that it occurs chiefly by arborization of the nerves which are still alive. It has been shown in experimental animals that when four fifths of the nerve fibers to a muscle have been cut, the remaining one fifth will arborize rapidly to such an extent that almost all the paralyzed muscle will soon be reinnervated.[32] This indicates that

31. Weiss, P., and Edds, M. V., Jr.: Spontaneous Recovery of Muscle Following Partial Denervation, Am. J. Physiol. **145**:587-607 (Feb.) 1946.

32. (*a*) Weiss and Edds.[31] (*b*) van Harreveld, A.: Reinnervation of Denervated Muscle Fibers by Adjacent Functioning Motor Units, Am. J. Physiol. **144**:477-493 (Sept.) 1945.

one original neuron may innervate at least five times as much muscle as it normally does, and possibly much more than this. In normal animals one axon leaving the spinal cord divides approximately one hundred and eighty times and innervates one hundred and eighty muscle fibers. After injury to the nerves, it is well known that the axons may divide still many more times, and there is logical reason, as well as experimental evidence, for the belief that the same mechanism is operative in poliomyelitis. Pathologic studies on animals infected with poliomyelitis have shown many instances of severe destruction of anterior horn cells with only transient paralysis.[33] Because each muscle fiber normally receives only one nerve ending,[34] recovery of the paralyzed muscle fibers in such instances could occur only by arborization.

Assuming arborization to be the cause of much of the recovery in poliomyelitis, one would expect every patient to experience a certain amount of recovery regardless of what type of treatment he is given; it has been found that this expectation agrees with actuality. The process of recovery by axonal arborization should proceed rapidly for the first few months because of intramuscular arborization and slowly for several years because of arborization at higher levels. The recovery in poliomyelitis, as predicted, does proceed rapidly for the first few months and then slowly for several years.

Electromyographic studies of recovering muscles also support the concept of arborization. After approximately three months of recovery, attempts to contract a weakened muscle will often cause simultaneous, synchronous action potentials in the opposing muscle.[28b] This has been explained on the basis of dissociated function in the spinal cord, but there are several important reasons for believing it to be a peripheral phenomenon. First, the fact that the impulses are actually synchronous in the two sets of muscles indicates an exactly common origin much as a single axon arborizing to both muscles. Second, this phenomenon does not occur during the period of maximal damage to the cord in the first two months but does appear concurrent with regeneration of nerves. Third, the same phenomenon occurs during recovery from injuries of peripheral nerves in which there is no damage to the cord whatsoever but in which arborization occurs greatly.

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33. (*a*) Sabin, A. B., and Ward, R.: Nature of Non-Paralytic and Transitory Poliomyelitis in Rhesus Monkeys Inoculated with Human Virus, J. Exper. Med. **73**:757-770 (June) 1941. (*b*) Bodian, D., and Howe, H. A.: The Pathology of Early Arrested and Non-Paralytic (Experimental) Poliomyelitis, Bull. Johns Hopkins Hosp. **69**:135-147 (Aug.) 1941.

34. Fort, W. B.: An Experimental Study of the Factors Involved in the Establishment of Neuromuscular Connections, Dissert., Chicago, 1940. Weiss, P., and Edds, M. V., Jr.: Spontaneous Recovery of Muscle Following Partial Denervation, Am. J. Physiol. **145**:587-607 (Feb.) 1946.

The Concept of Diffuse Partial Paralysis Versus Spotty Total Paralysis: Poliomyelitis infects the spinal cord in the same manner as chickenpox infects the skin, either with many small discrete lesions or with a few large confluent ones causing a diffuse partial paralysis of many muscles or total paralysis of a few spotty areas.[33b] The muscle areas experiencing total paralysis have no remaining axonal supply and therefore cannot recover by a process of arborization, but those with partial diffuse loss of axons obviously offer an ideal situation for recovery by this process. Such is the case during recovery from poliomyelitis; the muscle areas with spotty total paralysis exhibit little recovery, while recovery might be complete from an infection involving the entire body diffusely.[35]

Rapid Fatigue of Muscles: This has long been known to occur in muscles of patients convalescent from poliomyelitis. Because much of the phenomenon of fatigue is also known to be in the peripheral nerve endings rather than in the muscle fibers,[36] it follows that this clinical symptom is possibly a direct result of arborization. Stated differently, the nerve body located in the spinal cord is unable to nourish properly the greater number of nerve endings during excessive activity. Certainly there has been no other adequate explanation of fatigue of the muscles in patients convalescent from poliomyelitis. Electromyographic studies combined with electrical stimulation of motor nerves actually confirm the rapid fatigue of nerve endings in patients who have recovered from the disease.[37]

Crushing or Maceration of Nerves in Patients Convalescent from Poliomyelitis: This, also known as the Billig operation or neurotripsy, has been advocated because of the well known arborization effect after injury to the nerves. If arborization did not occur normally in patients convalescent from poliomyelitis, one would expect great success from such operations, but the available experimental evidence indicates that nerve crushing hinders the natural process of arborization rather than aids it.[31]

*C. Recovery of the Muscles.*—Preservation of the Muscle: Preservation of the muscle after denervation and before reinnervation is the goal of most modern treatment, but unfortunately little is known regarding this. The use of heat and of vasodilating drugs, by means of improved blood supply to the muscles, supposedly helps to preserve the muscle. Also, electrical stimulation has proved experimentally to

35. (*a*) Bodian and Howe.[33b] (*b*) Sabin and Ward.[33a]

36. Luco, J. V., and Rosenblueth, A.: Neuromuscular "Transmission-Fatigue" Produced Without Contraction During Curarization, Am. J. Physiol. **126**:58-65 (May) 1939.

37. Hodes, R.: Electromyographic Studies of Human Poliomyelitis, Am. J. M. Sc. **213**:509-510 (April) 1947.

be an aid to preservation of the muscles,[19b] but its use is too painful and elaborate for adequate use in cases of clinical poliomyelitis. The value of electrical stimulation appears to lie in the actual trophic effect of contraction of muscles on the denervated muscle much the same as the trophic effect of nerve stimuli, though anyone who has had experience with electrical stimulation will attest to its vasodilating effect, which might be a helpful factor. Electrical stimulation, contrary to popular belief, is not a new treatment in poliomyelitis but is at least a hundred years old.

Contracture: Contracture, along with fibrotic and fatty degeneration, takes place in varying degrees in denervated muscles of patients with poliomyelitis. For the first month or so the shortened muscle is plastic and can easily be stretched to normal length if the patient can stand the pain, but progressively the contracture becomes fibrotic in nature, offering extreme resistance to stretching after six months regardless of pain. Daily stretching of the muscles usually suffices to maintain their normal length. The contracting tendency lasts many months rather than a few weeks, requiring active treatment often for more than a year. The process of stretching is undoubtedly the most important function of the physical therapist in helping to preserve muscle integrity, for obviously a permanently contracted muscle is of no value to the patient. Also, bony deformities may result from contracture of muscles.

Reversion of the Atrophy: This is the first process in recovery of muscles after reinnervation, for atrophic muscles are almost lacking in strength despite innervation. Reversion of the atrophy results from the natural trophic action which nerve impulses and contraction have on muscle fibers. This process may take several months and may never be complete.

Hypertrophy: Hypertrophy of the innervated and reinnervated muscle fibers occurs almost universally in poliomyelitis and is the basis for exercise in treatment. A certain amount of hypertrophy occurs regardless of treatment because the body naturally substitutes functioning for nonfunctioning elements, thereby overusing certain muscle fibers, with resultant hypertrophy and increase in strength. By a process of controlled exercise, the hypertrophy may be made to occur more uniformly and more extensively than under normal conditions—another important and beneficial duty of the physical therapist. Because hypertrophy is dependent on exercise, the ultimate gain in strength and the duration of increasing increments depend on treatment. A twofold or a threefold increase in strength can be expected from this process over a period of several years if extensive exercise is carried out in the form of daily activity or of special treatment.

*D. The Process of Recovery as a Whole.*—Concurrent recovery occurs in the cord, nerves and muscle in the early days after the acute

disease, but after six weeks it appears that most recovery is peripheral in origin. Arborization of terminal nerves within the muscle bellies may add to the early recovery, whereas arborization of nerves close to the spinal cord may take as long as three years to affect the denervated muscle, a fact which possibly explains the long, slow recovery process in poliomyelitis. Hypertrophy of muscles may begin at any time provided sufficient exercise is instituted, for muscles affected by poliomyelitis may still be strengthened after ten years by appropriate exercise if hypertrophy has not already occurred from daily activity.

The ultimate amount of recovery cannot be predicted during the first six weeks of the disease, for the relative amount of paralysis that is due to reversible and nonreversible neuronal damage is still uncertain. In some cases virtually all the lesions are nonreversible, which means that little increase in muscle strength will occur during the phase of recovery of the cord, whereas in other cases notable recovery during the first month and a half often takes place because the neurons are only inactivated rather than completely destroyed.

Present evidence indicates that the process of arborization, which may occur over a period of several years, takes place in approximately the same amount in every case.[38] Therefore, the ultimate state of recovery would depend directly on the amount of strength remaining in the paralyzed muscles at approximately six weeks. In making these predictions, however, one must determine whether or not each muscle is paralyzed diffusely or in a spotty fashion, for muscles with areas of spotty total paralysis will show little or no recovery in these areas, making one's prediction for the muscle as a whole inaccurate. A formula expressing the final recovery, in percentage of normal, in terms of the six week status of the muscles may be expressed as follows:

$$L + \frac{100-L}{100} \times \frac{10L}{\frac{1 + 9L}{100}}$$

where L equals strength of muscle at six weeks expressed in percentage of normal.

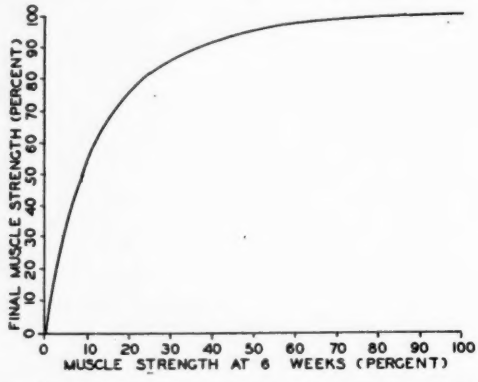
This formula was derived empirically from experimental evidence that arborization of an axon can occur sufficiently to produce at least five times as many nerve endings as it normally has and twofold hypertrophy may further strengthen the muscle. Obviously, the formula applies only to diffusely paralyzed muscles, but it may be applied to those with spotty total paralysis provided that the relative degree of spottiness is noted and proper deductions made.

The accompanying figure shows the formula graphically, from which it is predicted that a muscle which is 10 per cent normal at six

38. (*a*) Weiss and Edds.[81] (*b*) van Harreveld.[82b]

weeks will recover to a final state of approximately 57 per cent normal whereas a muscle which is 40 per cent normal will attain approximately 92 per cent normality. It follows that most muscles which have no more than 60 per cent paralysis will finally return practically to normal, though muscles with greater paralysis than this will show progressively greater degrees of permanent paralysis. Few quantitative studies have been made on recovery of muscles in poliomyelitis, but personal observation and the studies which are available indicate that the aforementioned formula is relatively accurate if applied properly.[39]

Isolated muscle reeducation, as practiced by many physical therapists, is based only on hypothetic concepts of the recovery process. This may be defined as a reestablishment of the pattern of spinal motor activity by a process of isolated muscle exercises. The description




Formula expressing final recovery in terms of the six week status of the muscles.

of recovery in this review was written with full cognizance of this theory which includes the internuncial cell theory of recovery and the theory of incoordination and mental alienation. These theories presume that there is a major physiologic disturbance in the pyramidal system proximal to the anterior horn cells though evidence for this premise is yet unproved. Personal experience has been convincing that the mild exercise associated with isolated muscle reeducation is the beneficial factor rather than the spirit of such treatment. Indeed, it is a well known physiologic fact that the human pattern of spinal activity is inherited from animal ancestry some million years back.

39. (*a*) Hipps, H. E.: Muscle Behavior Following Infantile Paralysis, Am. J. Surg. **53**:314-318 (Aug.) 1941. (*b*) McCarroll, H. R.: The Role of Physical Therapy in the Early Treatment of Poliomyelitis, J. A. M. A. **120**:517-519 (Oct. 17) 1942.

It is, therefore, highly presumptuous for any physical therapist to claim that the spinal pattern of activity can be changed by a special routine of exercise. The only direct evidence available demonstrates that ardent physical therapy is unable to affect spinal patterns but causes only changes in the brain cortex.[40] Discussion of isolated muscle reeducation at this time is therefore minimized, for far too much has already been written on the subject, and far too many physical therapists neglect exercise of the muscles in favor of educating them to do circus stunts.

Functional muscle reeducation, which may be defined as learning to use the unparalyzed muscles to their greatest advantage, is in a completely different category from isolated muscle reeducation. Obviously, the patient must learn to substitute his functioning muscles for paralyzed ones. He will learn to do this rapidly of his own accord if he is allowed sufficient range of activity. How soon this may be allowed to begin is greatly controversial. The major contraindication to early substitution of muscles is the possibility of causing deformity because of muscle imbalance. If the physical therapist carefully watches for such developments, however, there is no justifiable reason why functional reeducation cannot begin as soon as the acute disease is over. Should deformities begin to appear, they may be counteracted by stretching the overactive muscles or by the use of supportive apparatus rather than by inhibition of the patient's activity. By such a policy, the patient not only becomes rapidly habituated to his state of paralysis but also can psychologically accept a greater will to live.

## IV. A SUGGESTED REGIMEN OF TREATMENT BASED ON PHYSIOLOGIC CONCEPTS OF THE DISEASE

After a discussion of the pathologic physiology in poliomyelitis as well as of the process of recovery, certain suggestions for proper treatment of the disease become obvious. It must be stressed that the following principles are listed not as means of curing the patient but as aids in helping to make the natural process of recovery more rapid and more nearly complete.

A. Complete rest for the first two weeks, during the acute stage of the disease, is essential for preventing excessive spread of the virus. The virus is known to live in the spinal cord for at least this long and possibly longer, and there is much evidence that activity increases the spread of paralysis. This dictum of complete rest requires that all possible functions for the patient be carried out by the nurse and that he not even exert himself unnecessarily to turn in the bed without

40. Weiss, P., and Brown, P. F.: Electromyographic Studies on Recoordination of Leg Movements in Poliomyelitis Patients with Transposed Tendons, Proc. Soc. Exper. Biol. & Med. **48**:284-287 (Oct.) 1941.

help. To prevent stiffening of the muscles, it is essential to carry out mild passive exercises, but even these should be minimized or even completely neglected during the first three or four days while actual spread of the disease is taking place. The greater number of neuronal cells saved, the greater will be the final state of recovery.

B. Hotpacks have proved themselves to be of unquestionable value for relieving the pain of acute poliomyelitis and possibly also for preventing the muscle shortening. Heavy towels wrung out in hot faucet water are as effective as any method of preparing the packs, and personal experience has proved the steam-treated woolen packs, advocated by many physical therapists, to be almost useless in comparison. It must be remembered that the muscles rather than the skin need the heat; therefore, long-continued mild heat is much more effective than short-term blistering heat. Neostigmine may be used for its vasodilating effect, though this is hardly justified because the drug is dangerous and hotpacks are equally powerful. Even curare, to which amazing properties have been ascribed, is a vasodilator and probably is no better than properly applied hotpacks.

C. Serotherapy in the acute phase of the disease is a possibility though numerous trials with convalescent serum have proved it to be almost valueless because of inadequate dosage and wrong strain specificity. An infusion of several liters of pooled plasma is probably one of the best means of serotherapy,[41] for most normal persons have poliomyelitis antibodies, and large quantities of plasma are available. The plasma might also be of value in keeping edema of the cord at a minimum. There is experimental evidence that infusions of dextrose are also of value because poliomyelitis infection depresses glucose oxidation by neuronal cells,[42] possibly causing excess death of neurons when blood glucose is at a low level. Both of these procedures must be instituted at the earliest signs of paralysis in order to be of any value. Their trial, though not of certain value, is justified, for each neuron that is saved means increased strength in the recovered patient.

D. Only mild exercises and functional activity for the first two months of the disease are advisable. During this period the nutritional status of the body is often poor, and there exists a possible vasospastic ischemia of the muscles, which makes it inadvisable to overexercise the poorly nourished muscles.

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41. Barnum, G. L., and Bower, A. G.: Response of Acute Poliomyelitis to Large Doses of Plasma, U. S. Nav. M. Bull. **42**:730 (March) 1944.

42. (*a*) Racker, E., and Kabat, H.: Metabolism of Central Nervous System in Experimental Poliomyelitis, J. Exper. Med. **76**:579-585 (Dec.) 1942. (*b*) Racker, E., and Krimsky, I.: Inhibition of Phosphorylation of Glucose in Mouse Brains by Viruses and Its Prevention by Preparations of Diphosphopyridine Nucleotide, ibid. **84**:191-203 (Sept.) 1946.

E. Increasingly strenuous exercise should be pursued after the first two months of the disease, for by this time it is almost certain that all virus is gone, and the bodily functions, excepting muscle activity, are beginning to approach normal. Furthermore, experiments indicate strongly that early resistive exercises lead to the best recovery.

F. Vigilant stretching begun immediately after the acute stage of the disease is undoubtedly the major function of the physical therapist because the process of acute muscle shortening rapidly changes into fibrotic contracture. The optimum aim should be complete range of motion in all muscles within four months after onset of the disease because the shortened state of the muscles becomes increasingly irreversible after this time.

G. Complete functional use of the muscles should be allowed the patient after two months, and tendencies toward contracture should if possible be treated by counteractive stretching or by the use of various types of apparatus instead of limiting activity. An actual program of functional reeducation would likewise greatly shorten convalescence as well as aid the morale of the usually depressed patient with poliomyelitis.

H. Vocational therapy, a forgotten element in medical treatment, is essential for the rehabilitation of many patients with poliomyelitis. This does not mean occupational therapy as practiced in most hospitals, consisting of basket weaving, earring making and the making of jigsaw puzzles, but it refers to the teaching of an actual means to a livelihood such as stenography, the elements of education for prospective teachers, bookkeeping, accounting, business management and other uses of the intelligence to overcome physical handicaps. Happiness and the will to live are usually restored to the patient when he has been offered security and his way of life has been repatterned not to require physical abilities which no longer exist.

SUMMARY

1. The established principles regarding the etiology, pathogenesis and pathology of poliomyelitis have been briefly presented.

2. Relation of the pathologic physiology to symptoms has been more thoroughly discussed, and personal experience as a patient with poliomyelitis has been invoked in explaining several poorly understood symptoms. It is postulated that the pain, tenderness and muscle shortening are probably due to a generalized vasospastic condition secondary to lesions in the medulla.

3. The process of recovery is discussed, with particular emphasis on the arborization of peripheral nerves.

4. A regimen of treatment based on physiologic concepts of the disease has been briefly presented.

# EFFECTS OF SALICYLATES AND BENADRYL ON EXPERIMENTAL ANAPHYLACTIC HYPERSENSITIVE VASCULAR AND CARDIAC LESIONS

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IT IS WIDELY accepted that rheumatic fever is a disease of the heart, blood vessels and joints. The exact cause is not known, but the theory of allergy is attractive and supported by clinical, anatomic, bacteriologic and immunologic observations.

A great deal of experimental work has been done in the study of anaphylactic hypersensitive reactions in animals. The early work will be found described in the papers of Klinge,[1] Vaubel,[2] Knepper and Waaler,[3] and Knepper.[4] In 1943 Rich and Gregory[5] also demonstrated that lesions having basic characteristics of periarteritis nodosa could be produced in rabbits by the intravenous injection of sterile normal horse serum. Additional observations by these workers[6] revealed that anaphylactic hypersensitive reactions produced cardiac lesions which were morphologically similar to those of rheumatic carditis. Since Rich and Gregory pointed out this similarity, several papers[7] have appeared confirming their observations. We postulated that if the lesions produced by the anaphylactic hypersensitive reac-

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1. Klinge, F.: Beitr. z. path. Anat. u. z. allg. Path. **83**:185, 1929-1930.

2. Vaubel, E.: Beitr. z. path. Anat. u. z. allg. Path. **89**:374, 1932-1933.

3. Knepper, R., and Waaler, G.: Virchows Arch. f. path. Anat. **294**:587, 1934-1935.

4. Knepper, R.: Virchows Arch. f. path. Anat. **296**:364, 1935-1936.

5. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration that Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**:115-134, 1943.

6. Rich, A. R., and Gregory, J. E.: Experimental Evidence that Lesions with Basic Characteristics of Rheumatic Carditis Can Result from Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **73**:239-264, 1943.

7. (*a*) Procedure on Benadryl, Parke, Davis & Company, 1946. (*b*) Hopps, H. C., and Wissler, R. W.: The Experimental Production of Generalized Arteritis and Periarteritis (Periarteritis Nodosa), J. Lab. & Clin. Med. **31**:939-957, 1946. (*c*) Fox, R. A., and Jones, L. R.: Vascular Pathology in Rabbits Following

tions to foreign protein were comparable to those of rheumatic fever and pathologically indistinguishable from them, their production by a uniform method might offer a procedure for ascertaining the efficacy and rational use of the controversial antirheumatic drugs.

Rich and Gregory [6] stated that lesions may be produced in some rabbits by a single massive injection of horse serum. This method was tried by us first because of the shorter length of time involved. Rabbits were given intravenous injections of 10 cc. per kilogram of horse serum, observed for a febrile reaction and the aural flush and killed on the fourteenth day. By this method the lesions produced were so slight in degree and so few that it was impossible to ascertain their specificity.

It was then thought likely that the maintenance of a high concentration of antigen, to combine constantly with the specific antibodies as they became available, would give a greater chance for the production of anaphylactic changes in the myocardium. Hence the method was revised to include three massive injections (10 cc. per kilogram) over a period of thirty-one days. It was also found that the administration of 5 mg. per kilogram of "benadryl" (beta dimethylaminoethyl benzhydryl ether hydrochloride) intraperitoneally, five to ten minutes prior to the second and third injection of horse serum prevented fatalities from acute anaphylactic reactions, which some rabbits exhibit after repeated doses of horse serum. This method produced vascular lesions in the hearts of all the animals.

The following experiments represent: (1) a method which produces anaphylactic hypersensitive cardiac and vascular lesions in rabbits, (2) observations of the effects of salicylates on these lesions and (3) observations of the effects of "benadryl" [8] on these lesions.

## PROCEDURE

Sixty white male albino rabbits weighing from 1.5 to 2.4 Kg. each were housed in wire cages and fed commercial rabbit pellets and given water ad libitum. The rabbits were divided into the following four groups:

Group 1 was a control group composed of 15 animals which were dispersed among the animals of the other three groups but received no serum. Four of these

Administration of Foreign Proteins, Proc. Soc. Exper. Biol. & Med. **55**:294-295, 1944. (*d*) Smith, C. C.; Zeek, P. M., and McGuire, J.: Periarteritis Nodosa in Experimental Hypertensive Rats and Dogs, Am. J. Path. **20**:721-735, 1944. (*e*) Rich, A. R., and Gregory, J. E.: Experimental Production of Anaphylactic Lesions with the Basic Characteristics of Rheumatic Pneumonitis, Bull. Johns Hopkins Hosp. **78**:1, 1946. (*f*) Lichtenstein, L., and Fox, L. J.: Necrotizing Arterial Lesions Resembling those of Periarteritis Nodosa and Focal Visceral Necrosis Following Administration of Sulfathiazole, Am. J. Path. **22**:665-677, 1946. (*g*) French, A. J.: Hypersensitivity in the Pathogenesia of the Histopathologic Changes Associated with Sulfonamide Therapy, ibid. **22**:679-701, 1946.

8. The benadryl (injectable) was supplied through the courtesy of Parke, Davis and Company.

rabbits received "benadryl" intraperitoneally, and 6 rabbits received salicylate subcutaneously every eight hours.

Group 2, composed of 11 rabbits, was given intravenous injections of 10 cc. per kilogram of sterile normal horse serum (without preservative[9]). The ears were observed for the aural flush described by Fleisher and Jones.[10] Similar injections were repeated on the eleventh and twenty-first days. Five to ten minutes prior to the second and third injections 5 mg. per kilogram of "benadryl" was administered intraperitoneally. The animals were killed on the thirty-first day.

Group 3, composed of 22 rabbits, was treated in an identical manner to group 2, except that in addition the abdomen was shaved and each rabbit received 0.5 Gm. per kilogram of sodium salicylate per day as an isotonic solution into the subcutaneous tissues of the abdomen. Each daily dose was divided into thirds and given at eight hour intervals throughout the experiment. An additional injection of 50 mg. of ascorbic acid was given subcutaneously with each dose of salicylate. Blood was drawn three times weekly from veins in the leg, abdomen or ear for the determination of salicylate levels and prothrombin times. Each sample of blood was taken eight hours after an injection of salicylate. This report includes only the results in the rabbits surviving the full thirty-one days.

Group 4, composed of 12 rabbits, was also treated in an identical manner to group 2, but in addition the abdomen was shaved and 5 mg. of "benadryl" per kilogram was administered intraperitoneally every eight hours throughout the experiment.

Autopsies were performed immediately after the animals were killed. None of the organs showed noteworthy gross abnormalities. The tissues were fixed in a 4 per cent solution of formaldehyde. Sections including portions of the left atrium and left ventricle with pericardium, myocardium and mural and left atrioventricular valvular endocardium were taken. Each section of the heart measured, roughly 2 by 1 cm. The following stains were used: hematoxylin and eosin, Van Gieson's connective tissue method and Weigert's elastic tissue stain.

### NATURE OF VASCULAR AND CARDIAC LESIONS

*Vascular Lesions.*—All animals given multiple doses of sterile normal horse serum had noteworthy changes in arteries and arterioles, as indicated in tables 1, 2 and 3. The degree of development of the lesions varied considerably. In none of the animals were there changes in all cardiac vessels; even in those with the most pronounced vascular lesions there were many vessels which were without notable abnormality and appeared similar to the vessels of the control animals (figs. 1 and 2).

The arterial and arteriolar changes included swelling of endothelial cells, proliferation of the intima, alteration of the nuclei of muscle fibers, necrosis of the media and edema and cellular infiltration of all coats. In instances in which the lesions were most severe all these changes could be demonstrated. The alteration in the appearance of the muscle cells, however, was the only constant change in the animals

9. The horse serum was supplied through the courtesy of Lederle Laboratories.

10. Fleisher, M. S., and Jones, L.: Serum Sickness in Rabbits, J. Exper. Med. **54**:597, 1931.

receiving the multiple injections of sterile normal horse serum. The cardiac veins and venules showed only alteration in nuclei of the muscle cells, which was usually less notable than the change in the arteries and arterioles in the same animal.

The amount of intimal proliferation was directly proportionate to the degree of the other changes in the vessels. In some instances the

TABLE 1.—*Distribution of Cardiac Lesions and Degree of Reaction in Group of 11 Rabbits Receiving Repeated Massive Doses of Horse Serum*

| | Number of Animals Showing Degree of Reaction | | | | Total Number of Group Showing Positive Reaction |
|---|---|---|---|---|---|
| | + | ++ | +++ | ++++ | |
| Vascular | 1 | 7 | 3 | 0 | 11 (100%) |
| Myocardial | 6 | 2 | 0 | 1 | 9 (82%) |
| Valvular | 4 | 3 | 1 | 0 | 8 (72%) |
| Endocardial | 2 | 2 | 0 | 0 | 4 (36%) |
| Pericardial | 2 | 1 | 1 | 0 | 4 (36%) |

TABLE 2.—*Distribution of Cardiac Lesions and Degree of Reaction in Group of 12 Rabbits Receiving Repeated Massive Doses of Horse Serum and Treated With Sodium Salicylate*

| | Number of Animals Showing Degree of Reaction | | | | Total Number of Group Showing Positive Reaction |
|---|---|---|---|---|---|
| | + | ++ | +++ | ++++ | |
| Vascular | 1 | 2 | 8 | 1 | 12 (100%) |
| Myocardial | 3 | 5 | 4 | 0 | 12 (100%) |
| Valvular | 4 | 1 | 0 | 0 | 5 (41%) |
| Endocardial | 1 | 0 | 0 | 0 | 1 (8%) |
| Pericardial | 0 | 0 | 0 | 0 | 0 |

TABLE 3.—*Distribution of Cardiac Lesions and Degree of Reaction in Group of 12 Rabbits Receiving Repeated Massive Doses of Horse Serum and Treated with "Benadryl"*

| | Number of Animals Showing Degree of Reaction | | | | Total Number of Group Showing Positive Reaction |
|---|---|---|---|---|---|
| | + | ++ | +++ | ++++ | |
| Vascular | 3 | 5 | 2 | 2 | 12 (100%) |
| Myocardial | 6 | 4 | 0 | 1 | 11 (92%) |
| Valvular | 4 | 1 | 0 | 0 | 5 (41%) |
| Endocardial | 0 | 0 | 0 | 0 | 0 |
| Pericardial | 0 | 0 | 0 | 0 | 0 |

intimal proliferation was sufficient to reduce the size of the vascular lumens (fig. 3). In a few the endothelial cells were swollen and had hyperchromatic nuclei. Cellular infiltration of the intima was present in those with the most severe vascular lesions (fig. 3).

The changes in the media of the affected arteries and arterioles also varied in degree. In those with considerable changes the mediae were relatively thick and the lumens relatively small (fig. 4).

The constant and distinctive vascular lesion in the animals that received injections of horse serum was an alteration in the nuclei of

arterial and arteriolar muscle cells. Compared with the muscle cells in vessels of control animals (figs. 1 and 2), the nuclei were shorter, broader and more vesicular (figs. 5 and 6). In the nuclei of the altered muscle cell the chromatin was distributed in variable-sized and irregularly shaped masses. In many instances the chromatin was arranged in a central mass from which delicate fibrils radiated to or near to the nuclear membranes (figs. 5, 6 and 7). Such nuclei were indistinguishable from similar cells in perivascular connective tissue

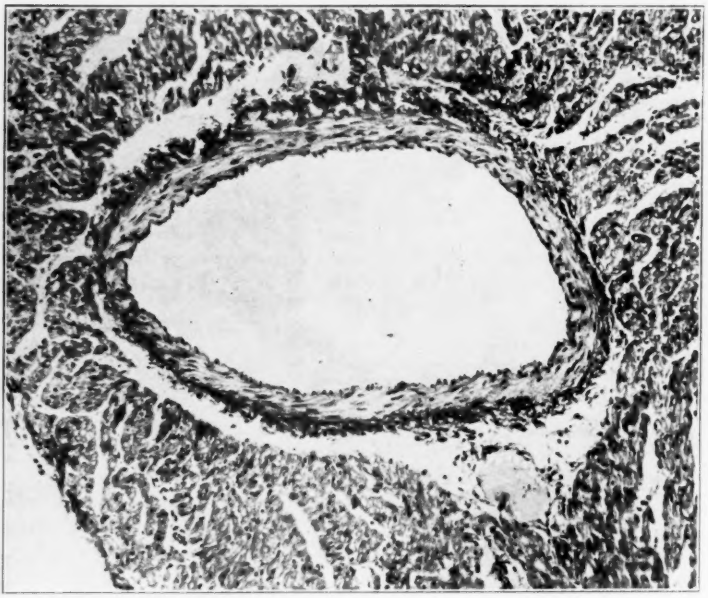

Fig. 1.—Normal artery in myocardium of control rabbit. × 152.

and are like the peculiar cells of the typical Aschoff body in human beings with rheumatic fever which are called Anitschkow myocytes or Aschoff cells. In 1 rabbit given injections of horse serum there were mononuclear and multinuclear giant cells in the media of small arteries (figs. 3 and 4).

Cellular infiltration was not constant, varied in amount and was particularly evident in the adventitia and the perivascular tissue. The exudative cells included polymorphonuclear neutrophils, eosinophils and large mononuclear cells.

*Cardiac Lesions.*—Microscopic changes similar to those that occur in human beings with acute rheumatic fever and identical with those described by Rich and Gregory[6] were present in a large percentage of the animals given multiple injections of sterile normal horse serum. Many of the rabbits had nonspecific myocarditis, but only those that received horse serum had lesions of the specific type. Characteristic changes were present in all coats of the heart, but the lesions were most abundant in the myocardium (tables 1, 2 and 3).

The lesions were characterized by cellular infiltration with one or more of the following: edema, swelling and degeneration of collagen fibrils and necrosis (fig. 8). Cellular exudation was a constant part

Fig. 2.—Portion of normal artery in heart of control rabbit. Nuclei of muscle cells are regular in shape and have homogeneous chromatin. × 874.

of all lesions. The foci of exudative cells were irregularly distributed in all the cardiac coats, being most conspicuous in the myocardium. The group of cells were usually perivascular in location (figs. 7, 8 and 9) and consisted of an occasional eosinophil, a few lymphocytes and many large mononuclear cells. Some of the mononuclear cells were atypical in that their nuclei were irregular in shape and deeply chromatic, but characteristically they had an abundance of slightly acidophilic cytoplasm and an oval vesicular nucleus (fig. 10). In many instances the nuclei had central masses and peripherally radiating fibrils of chromatin and were identical with Anitschkow myocytes (fig. 9). As already indicated, muscle cells in cardiac vessels of rabbits that received multpile injections of horse serum had nuclei of similar type.

Alterations of the nuclei of vascular muscle cells occurred in the absence of lesions like those of human rheumatic fever, but in no instance were there specific cardiac changes without altered nuclei in vessel walls.

In some instances exudative cells were at the periphery of circular foci of swollen and degenerated collagen fibrils (fig. 8). This was particularly evident in the valves, in which occasionally the nuclei were arranged in parallel groups (fig. 11).

Foci of necrosis were uncommon, being noted in only 2 of the rabbits. Lesions of the mural endocardium were particularly evident at the bases of valve leaflets and cusps. At such sites the cellular exudate was characteristic, and in 2 instances the presence of capillaries indicated organization (fig. 12).

The vascular and cardiac lesions were graded as to the degree of their development. An arbitrary classification (1 to 4 plus) was used.

The basis of grading was the degree of alteration of the nuclei of vascular muscle cells. Those graded as 1 plus had an occasional

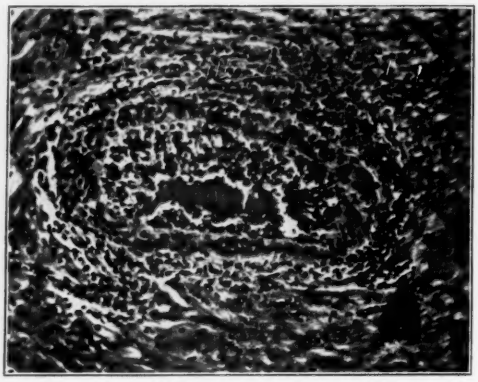

Fig. 3.—Small artery in myocardium of rabbit treated with horse serum. There is a notable cellular infiltration of all coats of the vessel and the perivascular tissue. The intima is thickened, and the lumen is narrowed. × 360.

vessel in which one or a few nuclei were altered. The ones classed as 4 plus showed many vessels (approximately 50 per cent of the cardiac vessels included in the sections) in which numerous cell nuclei had characteristic changes. Other lesions of cardiac arteries and arterioles, including swelling of endothelial cells, proliferation of the intima, necrosis of the media and edema and cellular infiltration of all coats were also noted and were directly proportionate to the degree of alteration of the nuclei of muscle cells. Some degree of focal necrosis, edema, interruption in the continuity of the elastica or cellular infiltration was noted in the media in the animals in which the lesions were

classified as 3 or 4 plus. In the ones with lesions classified as 1 and 2 plus, edema and cellular infiltration were sometimes slight in degree, but medial necrosis and intimal proliferation were not noted.

The reactions in the pericardium, myocardium and endocardium were graded in a similar manner. The size and number of foci of cellular infiltration were estimated. Animals with lesions graded as 1 plus showed only a few small groups of cells in the sections examined; those with lesions graded as 4 plus showed numerous groups of cells of

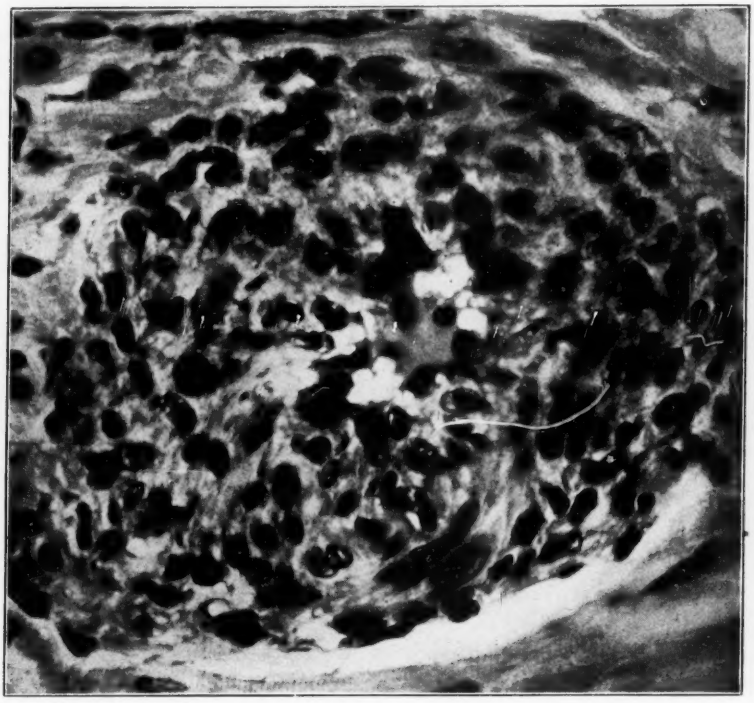

Fig. 4.—Small branch of coronary artery in rabbit treated with horse serum. The muscularis is relatively thick and the lumen small. The nuclei of muscle cells have irregularly distributed chromatin. Cells with giant nuclei are present in the inner portion. × 1,069.

variable size, along with edema, degeneration of connective tissue and occasionally necrosis.

## COMMENT

Salicylates have been used since 1881 in the treatment of clinical rheumatic fever. A widespread teaching in the past has been that sali-

cylates have a well-nigh specific effect in the rapid relief of swelling and pain. Nevertheless, there is no evidence that salicylates either control or shorten the fundamental disease process of the rheumatic infection. Many workers have noted depression of antibody formation by salicylate. Swift's [11] experiments on rabbits were concerned with the effect of salicylate on streptococcic immune bodies. He determined the effect of daily doses of sodium salicylate by mouth on the development of agglutinins and hemolysins in rabbits receiving intra-

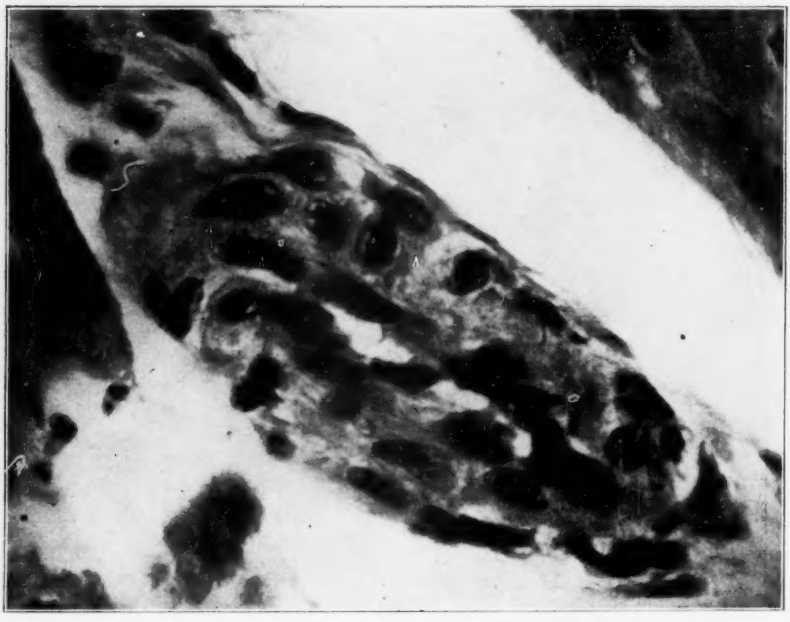

Fig. 5.—Small branch of coronary artery from rabbit treated with horse serum and "benadryl." In many of the muscle cells the nuclear chromatin is centrally placed. × 1,378.

venous injections of Streptococcus viridans. A lower titer of the antibody formation was thought to be due partially to some direct action on the antigen. Hanzlik [12] noted that salicylates were bound to the blood proteins to some extent, and Derick, Hitchcock and

11. Swift, H. F.: The Action of Sodium Salicylate upon the Formation of Immune Bodies, J. Exper. Med. **36**:735-760, 1922.

12. Hanzlik, P. J.: Actions and Uses of Salicylates and Cinchophen in Medicine, Medicine **6**:197-373, 1926.

Swift [13] noted that the serum of patients treated prophylactically with salicylates failed to precipitate horse serum. Homburger [14] has recently demonstrated that salicylates reduce the production of the anti-Rh antibody formation in guinea pigs and rabbits. Coburn and Knapp [15] studied the effect of salicylates in vitro on the precipitation of antigen and antibody and found that it inhibited the formation of precipitate, the degree of inhibition being related to the concentration of salicylate

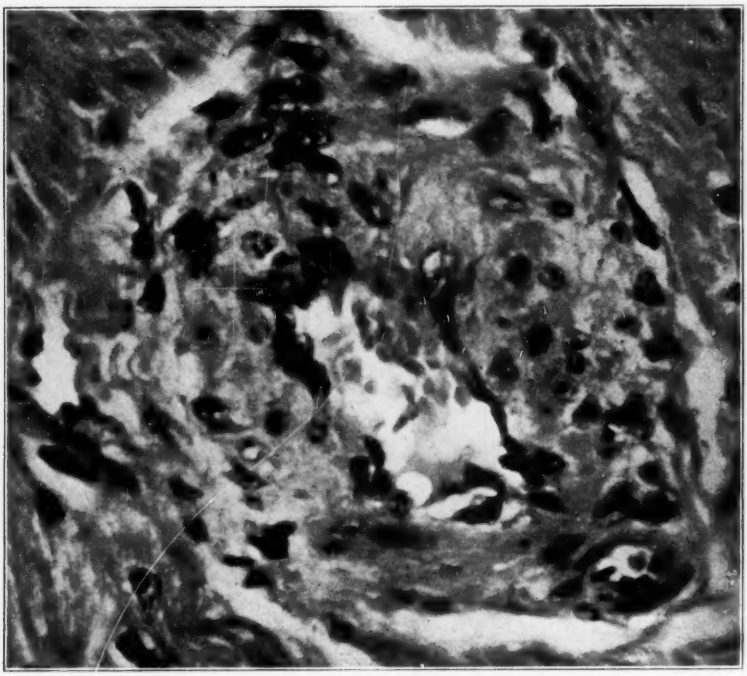

Fig. 6.—Small branch of coronary artery in rabbit treated with horse serum and sodium salicylate. The nuclear chromatin of muscle cells is centrally placed. Many of these muscle nuclei are like those of Anitschkow myocytes. × 1,079.

13. Derick, C. L.; Hitchcock, C. H., and Swift, H. F.: The Effect of Antirheumatic Drugs on the Arthritis and Immune Body Production in Serum Disease, J. Clin. Investigation **5**:427-440, 1928.

14. Homburger, F.: Sodium Salicylate Inhibiting Anti-Rh Immunization in Animals, Proc. Soc. Exper. Biol. & Med. **61**:101-102, 1946.

15. Coburn, A. F., and Knapp, E. M.: The Effect of Salicylates on the Precipitation of Antigen with Antibody, J. Exper. Med. **77**:173-183, 1943.

and the antigen-antibody ratio. Coburn and Moore [16] administered salicylates during streptococcic infections of the respiratory tract to patients who had had rheumatic fever and reported a reduced incidence of recurrent rheumatic attacks. On the basis of this evidence, Coburn [17] treated patients with active rheumatic fever with large doses of sodium salicylate and attempted to maintain salicylate blood levels of 36 to 37 mg. per hundred cubic centimeters. His reported results aroused

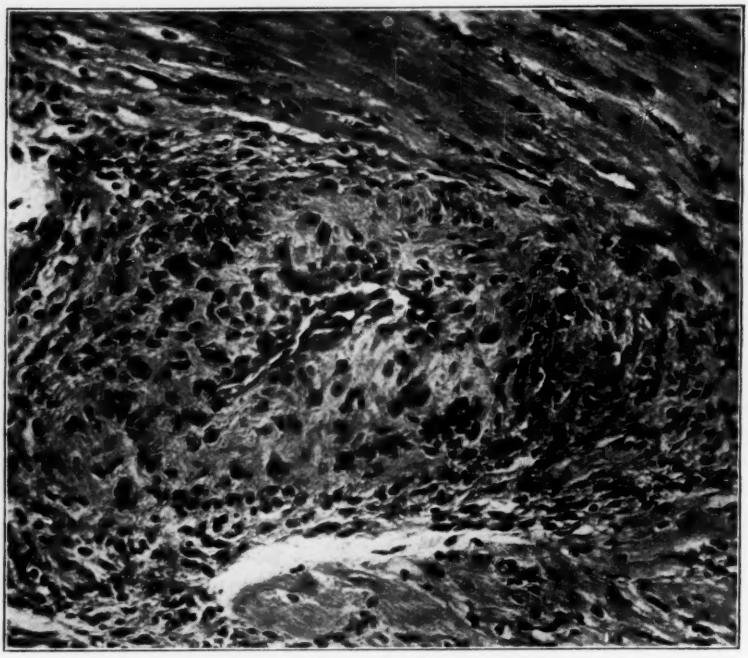

Fig. 7.—Small branch of coronary artery in rabbit treated with horse serum. The muscularis is thick and the lumen small. The chromatin in many muscle nuclei is central in position. There is perivascular infiltration with lymphocytes and large mononuclear cells. × 857.

much controversy in regard to the value of large doses of salicylates and their potential hazards.

16. Coburn, A. F., and Moore, L. V.: Salicylate Prophylaxis in Rheumatic Fever, J. Pediat. **21**:180-183, 1942.

17. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever: Rational Technique, Bull. Johns Hopkins Hosp. **73**:435-464, 1943.

Because of this controversy we became interested in the possibility of preventing or modifying the cardiac lesions morphologically similar to those of rheumatic fever that can be produced in the rabbit with multiple injections of horse serum. Triweekly determinations of plasma salicylate levels were made on the rabbits used in the experiment, the method of Brodie, Udenfriend and Coburn [18] being employed,

Fig. 8.—Portion of small artery and myocardium from rabbit treated with horse serum and sodium salicylate. The perivascular connective tissue is edematous and infiltrated with lymphocytes and large mononuclear cells. There are swelling and degeneration of collagen fibrils. × 950.

with the hope of obtaining and maintaining a plasma level of 36 to 37 mg. per hundred cubic centimeters. The salicylates were first administered by stomach tube, which proved to be unsatisfactory. A six to eight hour slow continuous intravenous drip method was tried next, and although satisfactory plasma levels were obtained at the immediate

18. Brodie, B. B.; Udenfriend, S., and Coburn, A. F.: Plasma Salicylic Acid, J. Pharmacol. & Exper. Therap. **80**:114-117, 1944.

conclusion of the infusion, all the salicylate had been excreted at the end of twenty-four hours. It was then decided to administer isotonic solution of sodium salicylate subcutaneously every eight hours, after the method of Clausen and Jager.[19] It was observed, as was reported by the aforenamed workers, that the plasma levels eight hours after the last injection varied markedly in different rabbits, although all were on the same dosage, and that the levels in individual animals

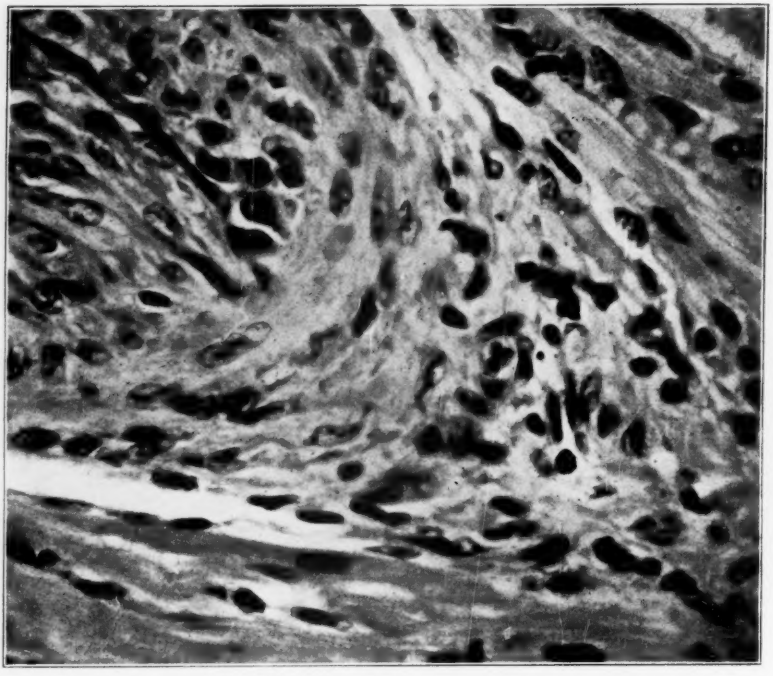

Fig. 9.—Portion of artery and myocardium from rabbit treated with horse serum and sodium salicylate. The perivascular connective tissue is infiltrated with lymphocytes and large mononuclear cells. Some of the cells are Anitschkow myocytes. × 1,069.

varied from day to day. It was also noted that salicylates were extremely toxic for the animals and that any rabbit whose eight hour plasma salicylate level reached 26 mg. per hundred cubic centimeters

19. Clausen, F. W., and Jager, B. V.: The Relation of Plasma Salicylate Level to the Degree of Hypoprothrombinemia, J. Lab. & Clin. Med. **31**:428-436, 1946.

died even though medication was discontinued. Three of the rabbits fatally intoxicated from salicylates had hemorrhage sufficient to have been instrumental in their death. The plasma levels of the rabbits which tolerated the administered dose of salicylate varied between 10 and 15 mg. per hundred cubic centimeters during the first few days of medication but dropped to zero or to a faint trace during the remainder of the course of treatment. Salicylate levels determined four hours

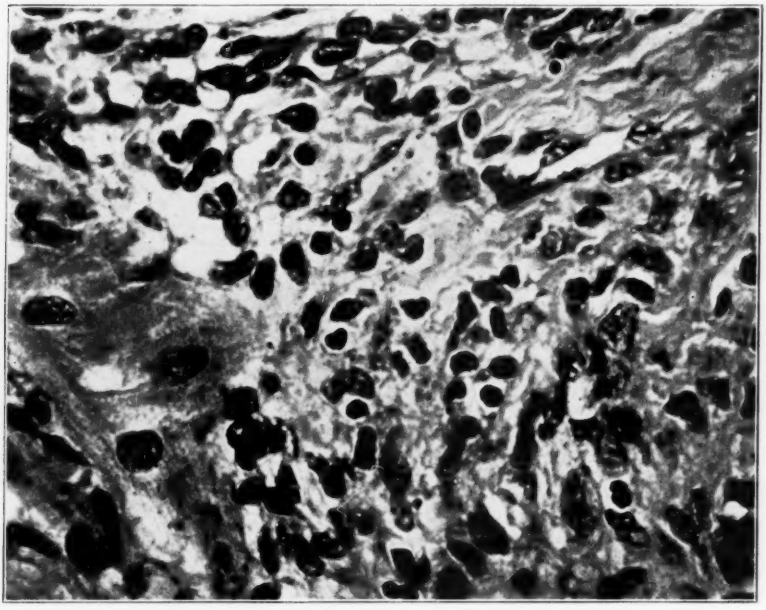

Fig. 10.—Portion of myocardium from rabbit treated with horse serum and "benadryl." The interstitial tissue is infiltrated with lymphocytes and large mononuclear cells. Some of the cells have giant nuclei. × 1,069.

after injections, when there were none at eight hours, were from 10 to 42 mg. per hundred cubic centimeters.

Mention is made in the literature [20] that ascorbic acid reduced the toxicity of salicylates. Consequently 50 mg. of ascorbic acid was administered subcutaneously three times a day to each rabbit during this experiment.

20. Pelner, L.: The Effect of Ascorbic Acid on the Sensitivity to Salicylates, J. Lab. & Clin. Med. **28**:28, 1943.

As Clausen and Jager [19] observed, the prothrombin activity was not materially affected by salicylates until plasma levels of 50 to 60 mg. per hundred cubic centimeters were obtained, and then all rabbits died. Hence, it was not certain whether the salicylates produced the prolonged prothrombin time or whether it was secondary to a depression of vital functions by the extreme toxicity. Vitamin K was not used in these experiments.

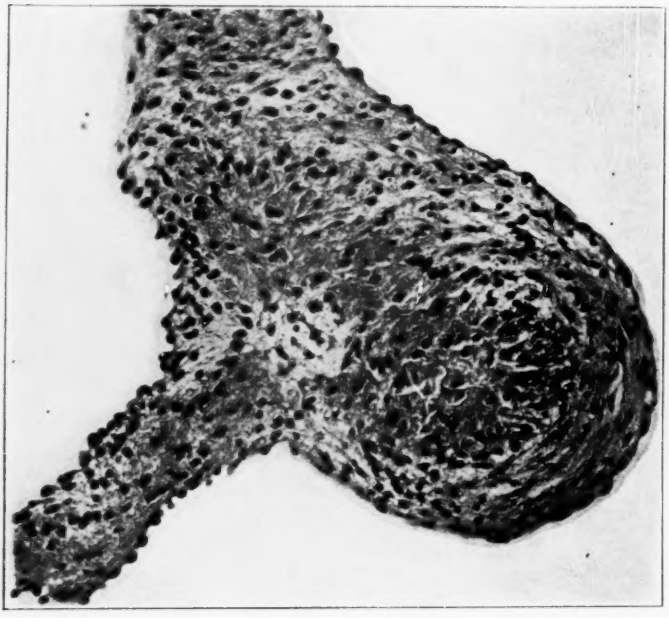

Fig. 11.—Portion of valve from rabbit treated with horse serum. There is one circular focus of degeneration of connective tissue with lymphocytes at the periphery. × 360.

As shown in table 2, the vascular and myocardial lesions in the rabbits which received salicylates and horse serum were just as numerous and possibly somewhat more pronounced in degree than those in the animals given only horse serum (table 1). This conforms to the recent clinical observations of Murphy [21] on human rheumatic fever.

21. Murphy, G. E.: Salicylate and Rheumatic Activity, Bull. Johns Hopkins Hosp. **77**:1-43, 1945.

In the experimental animals, however, salicylates appear to prevent to some extent the production of lesions of the mural endocardium, pericardium and valves.

### ANAPHYLACTIC HYPERSENSITIVITY AND "BENADRYL"

Rich [22] points out emphatically the difference between bacterial (tuberculin) and anaphylactic (arthus) types of hypersensitivity. He

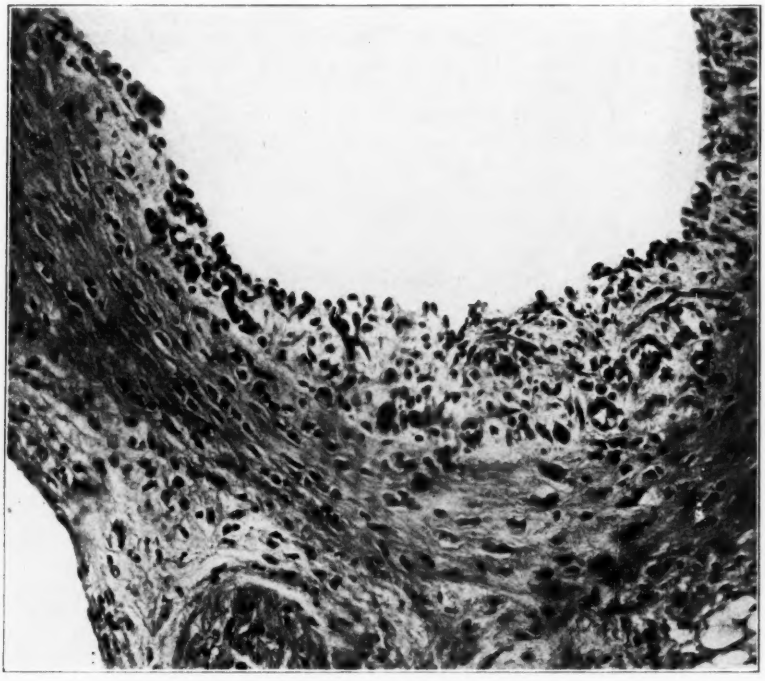

Fig. 12.—Lesion at base of valve from rabbit treated with horse serum. Cellular infiltration and capillaries are evident. × 288.

stresses the fact that in his experiments, in which sensitized rabbits were given horse serum, the cardiac and vascular lesions developed as a result of the anaphylactic type of hypersensitivity. According to Rich and Gregory,[23] rheumatic fever, periarteritis nodosa and serum sick-

22. Rich, A. R.: Significance of Hypersensitivity in Infections, Physiol. Rev. **21**:70-111, 1941. Rich and Gregory.[6]

23. Rich and Gregory (footnotes 5 and 6).

ness are probably manifestations of anaphylactic hypersensitivity. The lesions of the anaphylactic type are presumably produced by the union of antigen-antibody or by a substance liberated at the time of the merger. Zinsser [24] noted that antibodies could not be separated from proteins and were usually contained in the pseudoglobulin fraction of the serum. Heidelberger [25] concluded that antibodies were modified serum globulins. Sabin [26] injected "dye-protein" into rabbits and saw it in the macrophages. Coincident with the appearance of antibodies for the specific dye-protein in the serum, a shedding of the surface films of the macrophages without damage to the cells was observed. Sabin concluded that if the process were a general property of globulin-producing cells, any cell which could phagocytose antigen or allow its entrance into the cytoplasm might be the precursor of antibody. Also the antibody globulin thus produced might remain in the cell for a variable period and not necessarily be given up. Connective tissue cells, fibroblasts, lymphocytes, monocytes and possibly endothelial cells have been shown to produce globulin.

The normal immune response is for the cell to shed its globulin (antibody) and for that antibody to circulate in the blood stream. However, anaphylactic hypersensitivity is interrupted immunity. The globulin, or antibody, when formed in the cell, is held in situ instead of being shed, and when the circulating antigen comes in contact with the antibody (intracellular), a union occurs which is detrimental to the cell and a substance is released which causes focal changes throughout the body in the connective tissue, especially of the blood vessels in which the concentration is greatest. Culbertson [27] showed, with egg albumin in sensitized rabbits, that the fixed tissue precipitins function only when some of the antigen escapes union with the circulation precipitins.

In experimental hypersensitivity the toxic substance released by the union of antigens and their specific receptors in fixed tissue cells is the same, regardless of what the sensitizing antigen may be. Von Pirquet [28] first postulated that the antigen-antibody union formed a toxic sub-

24. Zinsser, H.: Resistance to Infectious Diseases, ed. 4, New York, The Macmillan Company, 1931.

25. Heidelberger, M.: Contributions of Chemistry to the Knowledge of Immune Processes, Medicine **12**:279-295, 1933.

26. Sabin, F. R.: Cellular Reaction to Dye-Protein with a Concept of Mechanism of Antibody Formation, J. Exper. Med. **70**:67-82, 1939.

27. Culbertson, J. T.: Role of Precipitin Antibody in Removal of Intravenously Injected Antigen, J. Immunol. **28**:279-295, 1935.

28. Von Pirquet, C. E.: Allergy, Arch. Int. Med. **7**:259-288 (Feb.); 383-436 (March) 1911.

stance which caused clinical manifestations. Many have been of the opinion that the "H" substance, or histamine, is the toxic substance released by damaged tissue cells. Dragstedt and Mead [29] found that histamine activity in the blood of dogs was abundant whenever anaphylactic reactions occurred and that it was present in sufficient amounts to account entirely for anaphylactic reactions.

On the assumption that the histamine which is presumably liberated by the reaction of antigen and fixed tissue antibody could be kept neutralized, the necrotizing lesions of the heart resulting from intravenous injections of horse serum should be inhibited. "Benadryl," an antihistamine drug, is known to prevent the lethal action of histamine in experimental animals and to antagonize many of the in vitro actions.[7a] The intravenous $L.D._{50}$ dose of "benadryl" for rabbits was demonstrated [7a] to be 10.5 mg. per kilogram. Five milligrams per kilogram, which is somewhat less than the $L.D._{50}$ dose, was administered by the intraperitoneal route every eight hours in this experiment. The action of "benadryl" begins within a few minutes after injection and continues for four to five hours. No determinations of plasma level were attempted. As can be noted from table 3, a conclusion can be drawn that "benadryl," in the dosage employed, exerts no appreciable protective or preventive action in rabbits as far as the development of vascular and myocardial lesions of an anaphylactic nature is concerned. However, "benadryl" apparently offers about the same protection against the production of lesions in the pericardium, endocardium and valves as was obtained with salicylates.

The results of the experiments recorded in this paper confirm the work of Rich and Gregory,[6] which pointed out the similarity of the lesions of rheumatic fever and those which occur in rabbits subjected to serum sickness, and tend to support the theory that hypersensitivity is an important etiologic factor in rheumatic fever.

It is worthy of note that in rabbits, as a result of multiple injections of sterile normal horse serum, there are not only cardiac lesions like those of rheumatic fever but there is also an alteration of muscle cells of cardiac vessels so that they are indistinguishable from Anitschkow myocytes. It seems possible, therefore, that the peculiar cell, the Anitschkow myocyte, which is common in rheumatic fever but not diagnostic of it may be an altered connective tissue cell or a muscle cell. The alteration of cells by horse serum to resemble the Anitschkow myocyte would support the theory of hypersensitivity.

29. Dragstedt, C. A., and Mead, F. B.: Peptone Shock, J. Pharmacol. & Exper. Therap. **59**:429-436, 1937. Dragstedt, C. A.: Anaphylaxis, Physiol. Rev. **21**: 563-587, 1941.

SUMMARY

1. The production of anaphylactic hypersensitive cardiac lesions in rabbits, reported by Rich and Gregory, has been confirmed, and a uniform method for their production has been outlined.

2. Sodium salicylate in the dosage given did not prevent the development of vascular and myocardial lesions of the anaphylactic hypersensitive type.

3. Sodium salicylate apparently prevented, to some extent, the development of pericardial, endocardial and valvular lesions.

4. "Benadryl," in the dosage given, did not prevent the vascular and myocardial lesions of the anaphylactic hypersensitive type.

5. "Benadryl" apparently prevented, to some extent, the developmental of pericardial, endocardial and valvular lesions.

# HEMOSIDEROSIS IN REFRACTORY ANEMIA

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THE DISCOVERY of iron and liver therapy has brought into prominence a type of primary anemia which fails to respond to any known treatment. This type has therefore been referred to as primary refractory anemia by Bomford and Rhoads,[1] who have further subdivided it into four types according to the histopathologic appearance of the bone marrow. These, with their clinically comparable conditions, are pseudoplastic anemia (partly mature, cellular marrow), aplastic anemia, or panmyelophthisis (hypocellular marrow), chronic granulocytopenia (immature cellular marrow) and myelosclerosis (fibrosis, sclerosis, and giant cell hyperplasia of the marrow).

With the lack of specific therapy, the main source of treatment is repeated blood transfusions. A dramatic observation in cases of refractory anemia treated with multiple blood transfusions has been the development of hemosiderosis of the liver, spleen and other organs.

An analysis of autopsy observations in 20 cases of refractory anemia from Bomford and Rhoad's series revealed that hemosiderosis of the liver was almost exclusively confined to patients treated with multiple blood transfusions. Conversely, hemosiderosis of the liver and spleen, and occasionally of the lymph nodes and bone marrow, developed in all patients so treated.

A review of the autopsy observations in 16 cases of refractory anemia in a personal series associated with extramedullary hematopoiesis (which forms the basis of another report) revealed that notable hemosiderosis developed in 3 patients treated with repeated blood transfusions. The 3 cases are here reported, and views on the pathogenesis of hemosiderosis are discussed.

## REPORT OF CASES

CASE 1.—P. E., a 70 year old white man who worked in the wallpaper industry, complained of fatigue seven months before his admission to the hospital. He continued to work, however, receiving from his physician intensive liver and iron

From the Department of Pathology, Toronto East General Hospital.

1. Bomford, R. R., and Rhoads, C. P.: Refractory Anemia, Quart. J. Med. **10**:175 (July) 1941.

therapy until he was admitted, ten months before his death, extremely weak and pale. His occupation did not entail working near paints or chemicals.

Physical examination revealed evidence of considerable loss of weight, striking pallor and enlargement of the spleen to 8 cm. below the costal margin. The liver and the lymph nodes were not palpable. Gastric analysis revealed achlorhydria. Laboratory investigation on his admission revealed a hemoglobin content of 32 per cent, a red blood cell count of 2,000,000, a white blood cell count of 4,000 and a platelet count of 236,000 per cubic millimeter. The differential count showed 21 per cent neutrophils, 4 per cent "stab" cells, 14 per cent juvenile cells, 13 per cent myelocytes and 1 per cent myeloblasts. Eight normoblasts and 4 erythroblasts per hundred white blood cells were seen. Urinalysis revealed no abnormalities. No occult blood was detected in the stools. The fragility test of the red cells showed a normal range. The icteric index was 9 units. Bence Jones protein was absent in the urine. The reaction to the Wassermann test of the blood was repeatedly negative. The blood nonprotein nitrogen was within the normal range. The patient's blood group was A, and he was Rh positive.

A sternal puncture was performed on two occasions, but no marrow was obtained. A trephination of the sternum was completed, and a diagnosis of myelofibrosis with sclerosis was made. Roentgenologic examination showed increased density of the lumbodorsal vertebrae, ribs, sternum, upper ends of the humeri and pelvis. A final diagnosis of osteosclerotic anemia with extramedullary hematopoiesis was formulated.

Treatment consisted in administration of 1,500 cc. of compatible blood, a high vitamin diet, liver extract, iron, folic acid (pteroyl glutamic acid) and brewers' yeast. The response was fleeting, and the patient had to be readmitted on two other occasions for treatment with infused blood in order to maintain a hemoglobin content between 60 and 70 per cent.

Eight months before his death, chronic pneumonia of unknown origin developed, which required several months to clear. An additional seven transfusions of 500 cc. of citrated blood each were given over a period of three months. The liver was then found to be enlarged to 5 cm. below the costal margin, and the spleen was palpable at the umbilicus. In the five month period before his death a total of twenty-eight transfusions of whole blood were given, but despite this treatment the patient gradually became weaker and had several severe attacks of epistaxis. On one occasion the platelet count was 20,000 per cubic millimeter.

Hepatic function tests at this time gave normal results. The blood calcium, phosphorus, phosphatase and protein contents were normal. During the ten month period of observation the patient received in all thirty-eight blood transfusions. During this time the hemoglobin value varied between 24 and 72 per cent, the white blood cell count between 940 and 6,400 per cubic millimeter and the platelet count between 20,000 and 236,000. The differential count of the white blood cells showed between 2 and 25 per cent myelocytes and myeloblasts. However, despite blood transfusions and an adequate diet, he gradually weakened and died.

*Summary of Autopsy Observations.*—Autopsy revealed osteosclerosis of the vertebrae, ribs, skull, pelvis and long bones, with associated myelofibrosis; extramedullary hematopoiesis (myeloid metaplasia) in the spleen, renal pelvis and lymph nodes; splenomegaly; hemosiderosis of the liver and spleen; generalized arteriosclerosis; pronounced atherosclerosis of the coronary arteries; diffuse fibrosis of the myocardium; atheroma of the aorta, with ectasia of the arch of the aorta; healed subapical tuberculosis of the upper lobe of the right lung; calculi of the prostate; accessory spleen.

Liver: The weight was 1,250 Gm. The consistency was normal and the capsule thin and transparent. The cut surface was purplish brown and showed some loss in pattern.

Spleen: The weight was 735 Gm. The capsule was thin, and the color was purplish blue. The cut surface did not bulge, was dark brown and revealed numerous spherical, dark red, well demarcated, bulging nodules, the largest measuring 2.5 cm. and the smaller ones averaging 0.5 to 1.0 cm. in diameter. The splenic pulp was fairly firm, and the malpighian follicles were not evident. Thrombosis of the vessels was absent.

The prussian blue reaction of slices of the liver and spleen was strongly positive (fig. 1).

*Summary of Microscopic Changes.*—Liver: The Kupffer cells were bulging with hemosiderin granules, whereas the parenchymal cells contained little pigment (fig. 2).

Spleen: Massive deposits of hemosiderin were diffusely scattered throughout the splenic pulp but were particularly dense in the dark red nodules. Extramedullary hematopoiesis was pronounced.

Fig. 1.—Fresh slices of liver of rich mahogany red and another slice which gave an intense prussian blue reaction for iron.

Lymph Nodes: Hemosiderin-filled macrophages were present in the sinuses in moderate amounts.

Kidneys: Extramedullary hematopoietic foci were present in the renal pelvis and contained large amounts of hemosiderin deposits.

*Chemical Analysis of Liver for Iron.*—Iron, as ferric oxide, was equal to 0.35 per cent of the wet weight of the liver. The total amount of iron in the liver was 4.4 Gm. The total amount of iron received in thirty-eight blood transfusions (400 cc. of whole blood each) was 8.2 Gm.

Sheldon placed the average iron content of nondiseased livers at 0.1 per cent of the wet weight.

Case 2.—A. J., a 62 year old woman, was first admitted to the hospital nine months before her death, complaining of anorexia, shortness of breath on slight exertion, loss of weight of 40 pounds (18 Kg.) in one year and pain in the lower part of the back and in the left upper abdominal quadrant for two years. Physical examination revealed only moderate enlargement of the spleen.

Laboratory investigation revealed a hemoglobin content of 31 per cent, a red blood cell count of 1,800,000, a white blood cell count of 4,400 and a platelet count

of 129,000 per cubic millimeter. The differential count of the white blood cells revealed 50 per cent neutrophils, 44 per cent lymphocytes and 8 per cent monocytes. The urine was normal, and a Kahn test of the blood gave a negative reaction. The nonprotein nitrogen content in the blood was repeatedly within normal limits.

The patient was treated with injections of liver, iron, vitamin B complex and amino acids, without response. Eight transfusions of 500 cc. of group A, Rh-positive, citrated blood were given, and roentgen radiation, totaling 400 r, was sprayed over the spleen on two occasions. The following month the hemoglobin content rose to 65 per cent and the red blood cell count to 3,000,000. The white blood cell count ranged between 2,000 and 3,700 per cubic centimeter. After roentgen therapy the spleen became somewhat smaller and the patient was dis-

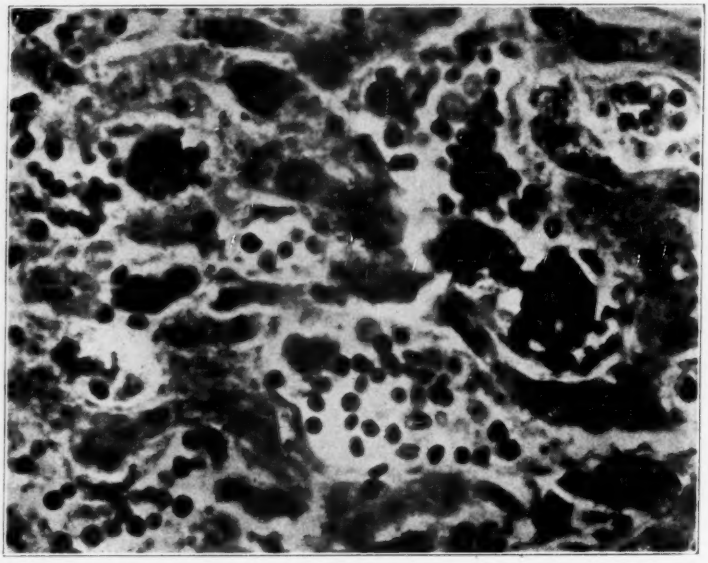

Fig. 2.—Kupffer cells in the liver sinusoids heavily laden with hemosiderin; parenchymal cells faintly dusted with siderotic granules. Turnbull's stain; × 660.

charged, only to be readmitted two months later. At this time the hemoglobin value was 20 per cent, the red blood cell count 1,100,000 and the white blood cell count 3,300, per cubic millimeter. Examination revealed a firm spleen and a tender liver, palpable 5 cm. below the costal margin. Small retinal hemorrhages were present.

Laboratory investigation revealed a normal van den Bergh reaction, an icteric index of 7 units, a reticulocyte count of 1 per cent and a normal reaction to the fragility test. The patient received another 800 r to the spleen and sixteen additional blood transfusions. The hemoglobin content rose to 65 per cent, the red blood cell count to 3,700,00 and the white blood cell count to 8,200.

Weekly blood transfusions were given until two weeks before her death, when the patient, feeling much weaker, was again hospitalized. A sternal puncture done

at this time revealed an extremely cellular marrow, with stem cells, erythroblasts, leukoblastic proliferation and increased hemosiderosis. No megaloblasts were found. Megakaryocytes were present. A diagnosis of refractory anemia with hypercellular marrow was made. The hemoglobin content fell to 14 per cent, the red blood cell count to 1,800,000 and the white blood cell count to 2,300, and the patient died.

A total of thirty-five blood transfusions had been given over a period of six months.

*Summary of the Autopsy Observations.*—Autopsy revealed pronounced, disseminated hyperplasia of the marrow, pronounced extramedullary hematopoiesis (myeloid metaplasia) of the spleen, splenomegaly, hepatomegaly, osteoporosis of the

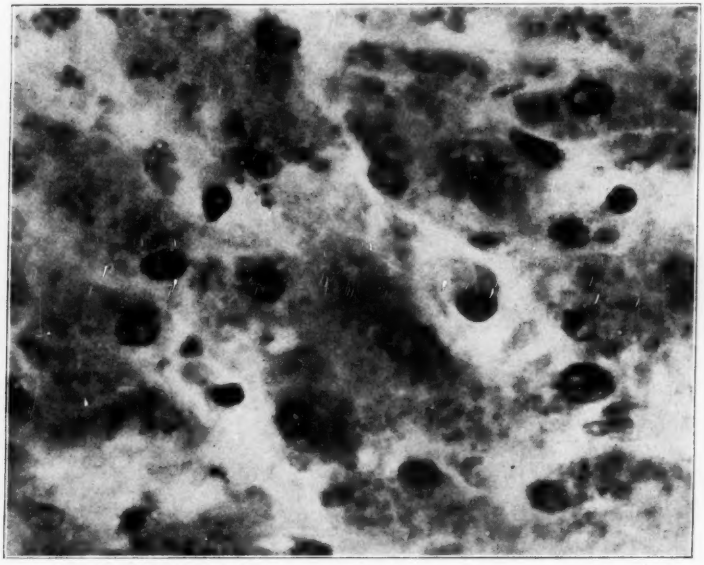

Fig. 3.—Cytoplasm of parenchymal cells of the liver charged with hemosiderin deposits. Hematoxylin and eosin; × 1,000.

vertebral bodies, heteroplastic hematopoiesis in the lumbar hemolymph nodes, hemosiderosis of the liver, infarcts of the spleen and cloudy swelling of the kidneys.

Liver: The liver weighed 2,385 Gm. Except for the dark nut red color, it was not remarkable.

Spleen: The spleen weighed 1,015 Gm. The cut surface was firm and had a mottled reddish and stone gray appearance, with dark red, subcapsular infarcts, the largest measuring 2 cm. in diameter and 1 cm. in depth.

*Summary of Microscopic Changes.*—Liver: A large amount of hemosiderin was deposited in the parenchymal cells but none in the Kupffer cells (fig. 3). No sclerosis or necrosis was present. Myeloid metaplastic foci were scattered throughout the sinusoids.

Spleen: Hemosiderin-laden cells were scattered through the splenic pulp but were particularly prominent in the areas of subcapsular scarring and infarctive change.

Bone Marrow: This was markedly hypercellular and partly mature, with moderately large amounts of hemosiderin. The cellular marrow was stuffed with a few stem cells, numerous erythroblasts and mature granulocytic groups.

Other Organs: No hemosiderin was present.

*Chemical Analysis of Liver for Iron.*—Iron, as ferric oxide, was equal to 0.52 per cent of the wet weight. The iron content of the liver was 12.5 Gm. The amount of iron received in thirty-five blood transfusions (400 cc. of whole blood each) was 7.6 Gm.

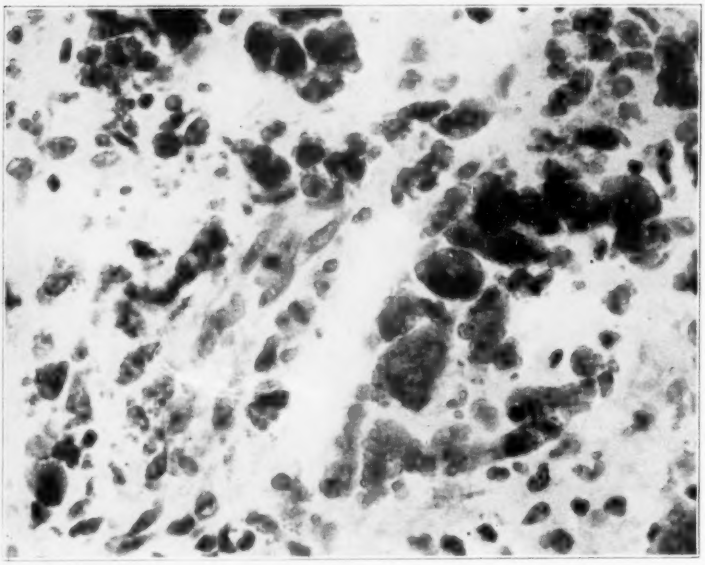

Fig. 4.—Coarse granules of iron deposited in the periportal regions of the liver. Fibroblastic nuclei are also shown. Hematoxylin and eosin stain; × 660.

Case 3.—M. N., a 66 year old white man, complained of tiredness eleven years before his death. Three and one-half years before death his condition began to deteriorate, with loss of weight and considerable enlargement of the spleen and liver. Laboratory investigation at that time revealed a hemoglobin content of 78 per cent, a red blood cell count of 3,700,000 and a white blood cell count of 7,000, with 2 per cent myeloblasts and myelocytes.

During the following three years he became extremely weak and lost more weight. The white blood cell count rose to 65,000 per cubic millimeter and then fell to 12,000, with 15 to 25 per cent immature myeloid cells. The spleen became greatly enlarged. Biopsy revealed fibrosis of the sternal marrow. The patient was treated with multiple blood transfusions in order to keep his hemoglobin between 60 and

80 per cent; in addition, he received mild irradiation to the splenic area, with some improvement of abdominal symptoms and a fall in the leukocyte count.

Two months before his death cystitis developed, with associated bladder calculi. After cystoscopic examination, pneumonia, cardiac decompensation, edema and nitrogen retention ensued. Cultures of the urine revealed Pseudomonas aeruginosa (Bacillus pyocyaneus). In spite of antibiotic treatment, the illness terminated in death.

A total of one hundred and fifteen blood transfusions had been given.

*Summary of Autopsy Observations.*—Autopsy revealed myelofibrosis; extramedullary hematopoiesis (myeloid metaplasia) of the spleen, lymph nodes and kidneys; pyogenic interstitial nephritis, necrotizing papillitis of the right kidney; portal cirrhosis of the liver, hemosiderosis of the liver, spleen and lymph nodes; nodular hyperplasia of the prostate; cystitis, and bronchopneumonia.

Liver: The weight was 2,780 Gm. The capsule was smooth and the outer surface uniform. The cut surface was chocolate brown, with a finely tessellated pattern formed by light brown nodules and darker brown sunken lines. The prussian blue reaction was moderate in intensity.

Spleen: The weight was 2,105 Gm. The color was mottled iron gray and light brown. The cut surface revealed a dark purple, uniform background with barely visible, evenly distributed, gray stippled markings. Infarction was absent.

*Summary of Microscopic Changes.*—Liver: Periportal fibrous tissue was increased in amount, but the lobular structure was well preserved. Massive deposits of hemosiderin granules were present in the connective tissue, hepatic parenchyma and large Kupffer cells (fig. 4).

Spleen: Hemosiderin was observed diffusely throughout the pulp but was particularly dense in the subcapsular areas. Extramedullary hematopoiesis was pronounced.

Lymph Nodes: The hemosiderin deposits were either patchy or diffuse and in some nodes mainly sinusoidal in distribution.

Bone Marrow: Myelofibrosis with associated osteosclerosis was present. Megakaryocytes predominated. Hemosiderin was present in small amounts in the reticuloendothelial cells.

Kidneys, Pancreas, Skin and Other Organs: No hemosiderosis was detected.

## COMMENT

Despite the varied picture of the marrow, the common denominator in these 3 cases was chronic marrow disease with refractory anemia and treatment with multiple blood transfusions. The common change in the liver and spleen observed post mortem was the intense hemosiderosis.

Hemosiderosis must be clearly distinguished from hemochromatosis, the former term denoting the deposition of iron pigment resulting from the destruction of red blood cells. The criteria adopted to distinguish these two conditions are those emphasized by Sheldon,[2] the most important feature undoubtedly being the difference in distribution of pigment, as noted in the spleen, bone marrow and kidneys. The abundant pigmentation of these organs in hemosiderosis is in decided contrast to

2. Sheldon, J. H.: Hemochromatosis, London, Oxford University Press, 1935.

the sparse distribution in hemochromatosis. The localization of pigment in the former condition speaks for a hemolytic origin. There is abundant evidence, both clinical and experimental, to show that an abnormal degree of hemolysis does not occur in hemochromatosis. Hemosiderosis of the kidneys, however, is not observed in cases of refractory anemia treated with repeated blood transfusions, in sharp contrast to what occurs in conditions in which an abnormal degree of hemolysis has taken place.

A history of nutritional deficiency was absent in the cases reported here. It was therefore concluded that the hemosiderosis in these cases had an origin different from that of the cytosiderosis of malnutrition in South African patients with pellagra described by Gillman and Gillman [3] and from that of the dietary hemosiderosis produced by Kinney [4] in rats.

The pathogenesis of the pigment deposition in cases of refractory anemia treated with multiple blood transfusions was not clear. Clinical and laboratory evidence of increased destruction of the patient's or donor's blood was lacking in the cases described here. Transfusion reactions were conspicuously absent. At no time did jaundice develop. Bomford and Rhoads [1] stated that there were cases of the refractory anemia group with a marrow picture of the partly mature, cellular type in which hemolysis (as indicated by an increased excretion of urobilinogen, a high reticulocyte count and the rapid disappearance of the transfused red blood cells) appeared to be particularly rapid, possibly due to a factor of hypersplenism. Hemolysis of transfused blood may, therefore, be a factor in the deposition of iron pigment. Chemical analysis of the liver for iron content, however, has revealed a greater amount of pigment in that organ alone than can be accounted for by hemolysis of all the transfused blood.

It is probable that the siderosis is due mainly to a disturbance in iron metabolism rather than to increased blood destruction. Because of inability of the diseased marrow to utilize iron, the ordinary slow destruction of red blood cells may result in an accumulation of pigment, which is deposited in the storage depots of the liver and spleen. The absence of hemosiderosis of the kidneys is added evidence against an abnormal degree of hemolysis being the etiologic factor and is in keeping with a "storage" phenomenon. Repeated blood transfusions simply increase the amount of circulating iron, which will eventually be deposited as hemosiderin rather than reutilized. If the refractory anemia is of sufficient duration, large quantities of iron may therefore accumulate.

3. Gillman, J., and Gillman, T.: Structure of Liver in Pellagra, Arch. Path. **40**:239 (Oct.) 1945.

4. Kinney, T.: Read before the American Association of Pathologists, Philadelphia, March 13, 1948.

The situation is probably somewhat analogous to that observed in pernicious anemia, in which it is now felt that the hemosiderosis is not due purely to a hemolytic anemia resulting from excessive blood destruction but is caused by the inability of the marrow to utilize the normally produced pigment in the absence of the hemopoietic principle.

The possibility exists that some of the hemosiderosis may be the end result of a local tissue purpura. The splenic nodules in case 1, which were heavily charged with hemosiderin, may represent the morphologic manifestation of this phenomenon.

A rare occurrence in patients with refractory anemia who have received multiple blood transfusions is the coexistence of a condition indistinguishable from hemochromatosis.[5]

Bomford and Rhoads [1] expressed the belief that damage to the liver in varying degrees is an important etiologic factor in refractory anemia. The hepatic dysfunction is expressed by a failure of the detoxication mechanism. This results in a direct assault on the marrow by noxae, terminating as chronic marrow disease of refractory anemia. It is also possible that chronic damage to the marrow and liver may follow a common destructive agent. According to Zeltmacher and Bevans,[5d] the increased deposits of iron in the presence of cirrhotic damage of the liver may produce a picture indistinguishable from that of hemochromatosis. These authors stated, however, that, in contrast to idiopathic hemochromatosis, increased hemolysis is a factor in the evolution of hemochromatosis associated with refractory anemia.

Despite the association of cirrhosis and pigmentation in case 3, a diagnosis of hemochromatosis could not be made, since many of the important features of this condition were lacking. Whether intense hemosiderosis of the liver may be an etiologic factor in the production of cirrhosis has long been unanswered. As far as the liver is concerned, the absence of cirrhosis in cases of intense hemosiderosis, as seen in congenital hematoporphyrinuria [2] and in pernicious anemia treated with multiple blood transfusions,[6] is against the likelihood of the fibrosis being

5. (*a*) Kark, R. M.: Two Cases of Aplastic Anemia, Guy's Hosp. Rep. **87**:343 (July) 1937. (*b*) Mackey, R.: Unusual Case of Aplastic Anemia with Organ Changes Resembling Hemochromatosis, M. J. Australia **1**:172 (Feb. 7) 1942. (*c*) Bomford and Rhoads.[1] (*d*) Zeltmacher, K., and Bevans, M.: Aplastic Anemia and Its Association with Hemochromatosis, Arch. Int. Med. **75**:395 (June) 1945. (*e*) Bethell, F. H.; Sturgis, C. C.; Rundles, R. W., and Meyers, M. C.: Blood: A Review of the Recent Literature, Arch. Int. Med. **76**:239 (Oct.) 1945. (*f*) Levinson, S. A., and Limarzi, L. R.: Agnogenic Myeloid Metaplasia of the Spleen, Am. J. Clin. Path. **17**:449 (June) 1947.

6. Yates, J. L., and Thalhimer, W.: Treatment of Pernicious Anemia, J. A. M. A. **87**:2156 (Dec. 25) 1926. Jones, H. W.: Prolonged Blood Transfusions in Pernicious Anemia, ibid. **86**:1673 (May 29) 1926.

caused by the pigment. The failure to produce cirrhosis experimentally, in spite of considerable pigment deposition, by long-continued and heavy doses of iron,[7] is in agreement with this. Cirrhosis, therefore, cannot be regarded as a secondary lesion produced directly by the irritation of pigment, but the possibility exists that the pigment may act indirectly by causing parenchymal degeneration, to which the fibrosis is secondary. It is most likely, however, that the hepatic cirrhosis is produced independently of the pigmentation.

Although no final answer to the question of the pathogenesis of the pigment deposition has been given, it was believed pertinent that attention should be drawn to the development of hemosiderosis in this day and age of multiple blood transfusions.

## SUMMARY

1. Three cases of pronounced hemosiderosis associated with refractory anemia which was treated with multiple blood transfusions are reported.

2. Views on pathogenesis are discussed.

Dr. C. M. Jephcott, of the Ontario Department of Health, made the chemical analyses, and Dr. W. S. Hartroft, of the Banting and Best Department of Medical Research, aided in the photomicrography. Permission was received from Prof. W. Boyd to publish case 3.

University of Toronto.

7. Cappell, D. F.: Late Results of Intravenous Injection of Colloidal Iron, J. Path. & Bact. **33**:175 (Jan.) 1930. Polson, C. J.: The Fate of Colloidal Iron Administered Intravenously: II. Long Experiments, ibid. **32**:247 (April) 1929.

# Progress in Internal Medicine

## SYPHILIS

### A Review of the Recent Literature

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THIS IS the thirteenth annual review [1] of the literature on syphilis. Its content is selected from publications, mostly American, which have appeared during the year ending July 1, 1948. A mere trickle of material of interest is to be found in foreign journals. A marked, and possibly permanent, shift from metal chemotherapy to penicillin in the treatment of syphilis, the tentative crystallization of optimal methods of penicillin treatment in various manifestations of syphilitic disease as a result of nearly five years of study and an intense and diverse activity in the field of serodiagnosis appear to have been dominating interests during the past year.

1. (*a*) Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **56**:1015 (Nov.) 1935. (*b*) Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **58**:901 (Nov.) 1936; (*c*) **60**:887 (Nov.) 1937. (*d*) Padget, P.; Sullivan, M., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **62**:1029 (Dec.) 1938. (*e*) Moore, J. E., and Mohr, C. F.: Syphilis: A Review of the Recent Literature, ibid. **64**:1053 (Nov.) 1939. (*f*) Mohr, C. F.; Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **66**:1112 (Nov.) 1940. (*g*) Mohr, C. F.; Padget, P.; Hahn, R. D., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **69**: 470 (March) 1942. (*h*) Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **70**:836 (Nov.) 1942; (*i*) **72**:635 (Nov.) 1943. (*j*) Mohr, C. F.; Scott, V.; Hahn, R. D.; Clark, E. G., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **74**:390 (Nov.); 457 (Dec.) 1944. (*k*) Mohr, C. F.; Scott, V.; Hahn, R. D., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **77**:332 (March) 1946; **77**:428 (April) 1946. (*l*) Reynolds, F. W., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **80**:655 (Nov.); 799 (Dec.) 1947; **81**:85 (Jan.) 1948.

### HISTORY OF SYPHILIS

Truffi [2] presents a detailed story of the life of Hieronymus Fracastor, better known for poetic than for scientific works. Besides the immortal poem *"Syphilis Sive Morbus Gallicus"* (Verona, 1530), Fracastor wrote other treatises on medicine. One of the best known of his other publications is *"De Contagione et Contagiosis Morbis,"* published at Venice in 1546. Here for the first time he expressed the idea that the principle of contagion resides in vital germs (which he called *"seminaria morbi"*) capable of generating the same disease when transferred to another person. The work contained a brief prose treatise on syphilis in which Fracastor concluded that only exceptionally was syphilis transmitted indirectly (i. e., by fomites) and that it was never transmitted at a distance. He clearly indicated the long incubation period of the infection and described the primary lesion as well as the symptoms of secondary syphilis.

### EXPERIMENTAL SYPHILIS

Stokes and Beerman [3] briefly review the literature on some unsolved problems in the biology of syphilitic infection in a paper which should be consulted in the original by workers in this field.

*The Rate of Multiplication of Treponema Pallidum.*—In an article of great importance, Magnuson, Eagle and Fleischman [4] present data on the minimal infective inoculum of Treponema pallidum and the bearing of their findings on the multiplication time of the organism. Utilizing ingenious technical methods, they have shown that on intratesticular inoculation 1 to 2 spirochetes are regularly infectious for rabbits. Larger numbers of organisms (200,000) were required regularly to produce chancres when inoculation was by the intracutaneous route, though only 2 spirochetes so introduced resulted in chancres in 47 per cent of the animals tested. The authors say:

> [There was] an approximately linear relationship . . . between the size of the intracutaneous inoculum, plotted logarithmically, and the time required for the appearance of a dark-field positive lesion. It is a reasonable surmise that the smaller inocula must multiply for a longer period in vivo before enough organisms are present to cause an inflammatory reaction. If that interpretation is correct, the experimental data permit an evaluation of the average rate of multipliction of spirochetes in vivo.

2. Truffi, M.: The Story of Hieronymus Fracastor: Renaissance Physician and Originator of the Term "Syphilis," Urol. & Cutan. Rev. **51**:515 (Sept.) 1947.

3. Stokes, J. H., and Beerman, H.: Some Problems in the Biology of the Syphilitic Infection, Am. J. M. Sc. **215**:461 (April) 1948.

4. Magnuson, H. J.; Eagle, H., and Fleischman, R.: The Minimal Infectious Inoculum of Spirochaeta Pallida (Nichols Strain), and a Consideration of Its Rate of Multiplication in Vivo, Am. J. Syph., Gonor. & Ven. Dis. **32**:1 (Jan.) 1948.

The following discussion is based on the skin inoculation experiments, since the earliest appearance of the skin lesion is more easily detected than is the testicular lesion, and the data with respect to incubation period are therefore more reliable.

Three assumptions must be made: (1) that *S. pallida* divides by the fission of one spirochete into two spirochetes; (2) that nearly all of the spirochetes survive during the incubation period of the disease; and (3) that the average number of spirochetes which must finally be present in order to initiate the appearance of the primary lesion is independent of the number of spirochetes originally inoculated, within the range 1 to 200,000. . . .

With each successive tenfold decrease in the number of spirochetes inoculated, there was an average increase of 4.1 days in the incubation period. The suggested explanation is that it requires 4.1 days for the organisms to multiply tenfold, and thus compensate for the difference in inoculum. If we assume that each spirochete divides into two spirochetes, there were 3.3 divisions in the 4.1 days ($2^{3.3} = 10$), which gives an average of 1.24 days or thirty hours for each division.

It must, however, be emphasized that this is an overall, average figure. In rabbits inoculated at multiple sites with varying numbers of spirochetes, the increment in the incubation period with each tenfold difference in the size of the inoculum varied within extraordinarily wide limits. . . . The *average* increment in a group of rabbits was, however, reasonably constant. As the inoculum was decreased step-wise from 200,000-20,000-2,000-200-20-2 spirochetes, the difference in the incubation period (in the same rabbit) for each tenfold difference in inoculum averaged 3.7, 3.7, 4.0, 5.6, and 5.8 days, respectively.

It is of interest in this connection that in the treatment of experimental syphilis when penicillin in aqueous solution was administered every 2, 4, 8 to 16, or every 24 hours to the same total number of injections, the optimum interval between injections, permitting cure with the smallest amount of penicillin, was 8 to 16 hours. Injections given at 24-hour intervals were significantly less effective, in that larger amounts of penicillin were then required for cure. Two possible explanations suggest themselves: (1) that organisms damaged but not killed by the drug may recover if too long an interval is allowed between injections; and (2) that the organisms may multiply sufficiently between injections to counteract the therapeutic action of the drug. In experimental pneumococcal infections of mice, three times as much penicillin was required for cure if four injections were given at nine-hour intervals than if they were given at three-hour intervals, reflecting the rapid growth of these organisms in the penicillin-free interval. With spirochetes, however, this effect was apparent only when the interval between injections was increased to twenty-four hours; corresponding to the slower rate of division of this organism in vivo.

Cumberland and Turner,[5] using a slightly different but none the less quantitative technic of intratesticular inoculation in rabbits, also estimate the multiplication time of T. pallidum to be thirty-three hours, a figure corresponding closely with the figure of thirty hours obtained by Magnuson and his co-workers.[4] These data are of great practical importance in the penicillin therapy of syphilis in man, as will subsequently appear.

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5. Cumberland, M. C., and Turner, T. B.: The Rate of Multiplication of Treponema Pallidum in Normal and Immune Animals, read at a Symposium of the Syphilis Study Section, N. I. H., Washington, D. C., April 8, 1948.

*The Growth Requirements of the Reiter Strain of T. pallidum.*—Whiteley and Frazier [6] studied the growth of the Reiter strain of cultured nonvirulent spirochetes in mediums of various complexity. They determined the turbidimetric rate of growth and the number of subcultures supported by each medium. Growth could be maintained for nine subcultures in a medium consisting of a mixture of amino acids, sodium thioglycollate, glucose, vitamins, dipotassium phosphate and serum albumin. This medium has been used to study turbidimetrically the effect of other nutrients and the effect of the action of penicillin and oxophenarsine hydrochloride on the growth of the organism. In the past the in vitro action of treponemicidial agents has been evaluated on the basis of changes in count, morphology and motility of spirochetes. The mediums devised in the course of the present study may be used for investigation of the sensitivity of the Reiter strain to these agents.

The mediums described for the cultivation of the Reiter strain were also inoculated with testicular material from rabbits with active orchitis following inoculation with the Nichols strain of virulent T. pallidum. All attempts at cultivation of virulent organisms were unsuccessful.

*The Duration of Life of T. Pallidum Under Certain Artificial Conditions.*—As a result of a review of observations of others and of his own controlled experiments with rabbits, Probey [7] concludes that (1) T. pallida suspended in sodium chloride solution and blood serum became avirulent and were apparently killed during the deep freezing and drying process, (2) in rabbits inoculated with restored dried material evidence of syphilitic infection failed to develop during approximately one hundred and forty days of observation; three successive subtransfers, observed for thirteen, seven and nine months respectively, also gave negative results and (3) the danger of transfusion syphilis appeared to be eliminated with the use of processed (frozen and dried) human plasma or of serum containing not more than 1 per cent moisture.

Lumsden [8] received capillary tube samples of material from genital lesions after the tubes had been in transit for several days. The question arose as to whether or not such material was satisfactory for the dark field diagnosis of early syphilis. He investigated, therefore, the viability of T. pallidum in similar sealed preparations made by him from lesions reacting positively to dark field examination and later examined at various intervals. When these tubes were stored in the incubator at

6. Whiteley, H. R., and Frazier, C. N.: A Study of the Nutritional Requirements of the Reiter Strain of Treponema Pallidum, Am. J. Syph., Gonor. & Ven. Dis. **32**:43 (Jan.) 1948.

7. Probey, T. F.: Loss of Virulence of Treponema Pallidum During Processing of Dried Blood Serum, Pub. Health Rep. **62**:1199 (Aug. 15) 1947.

8. Lumsden, C. E.: Viability of Treponema Pallidum, Lancet **2**:827 (Dec. 6) 1947.

37 C., T. pallida were said to have remained viable for from six to ten days. When stored at room temperature the organisms remained viable for ten to thirteen days. Several additional slide preparations were sealed with soft paraffin and stored at room temperature or at 37 C. In each case T. pallida remained viable for eight to fourteen days. Lumsden thinks it is not sufficiently appreciated that T. pallidum is viable for long periods outside the human body. In human necropsy material kept under refrigeration spirochetes have been found to be motile after forty-eight hours. Enormous numbers of T. pallida may be present in macerated fetuses, suggesting that the organism can multiply in dead tissues under anaerobic conditions.

Although Lumsden's observations concerning the viability of T. pallidum in human necropsy material are well known, his experimental data are at variance with observations of other workers. In attempts to cultivate T. pallidum, even in the presence of tissue extracts, viability has been noted consistently to persist for much shorter periods.

*Immunity.*—The present experiments by Eagle and Fleischman [9] throw no further light on the mechanism of immunity in syphilis. They do constitute strong evidence that so-called reagin may be simply an antibody to T. pallidum. The authors summarize their work as follows:

> The intravenous injection into rabbits of suspensions of dead *T. pallidum* derived from rabbit testicular chancres regularly caused the appearance of Wassermann and flocculation antibodies in significantly increased titer. Control suspensions of cultured treponemes (Reiter strain) added to extracts of normal testes were ineffective. This suggests that the Wassermann and flocculation reagin elaborated during syphilitic infection may be an antibody to *T. pallidum* which happens to cross-react with alcoholic extracts of mammalian tissue.
>
> The antisera did not cause the agglutination of suspensions of pathogenic T. pallidum, living or dead, did not give specific complement fixation with those suspensions, and did not usually cause the living treponemata to lose their infectiousness.
>
> Animals immunized with such aqueous suspensions for as long as 4 months, or with organisms suspended in water-in-oil emulsion, were not demonstrably resistant to infection. As few as ten living organisms inoculated intradermally into animals "immunized" with as many as 38 billion dead treponemata regularly produced typical dark field positive infections; and two of five animals inoculated intratesticularly with ten organisms were also infected.

The authors discuss in some detail the question of the significance of the production of antibodies cross reacting with a nonspecific (beef heart lipid) antigen and the nonappearance of specific antibodies against the organism used as antigen. They suspect, although they agree that they cannot definitely prove, that "reagin" elaborated in these experiments and during syphilitic infection represents a true antibody response to pathogenic T. pallidum.

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9. Eagle, H., and Fleischman, R.: The Antibody Response in Rabbits to Killed Suspensions of Pathogenic Treponema Pallidum, J. Exper. Med. **87**:369 (May) 1948.

Magnuson and his associates have also been concerned for several years with attempts at artificial immunization of animals against syphilitic infection. These experiments have been carried further in the present study by Magnuson, Halbert and Rosenau,[10] who utilized quantitative methods of immunization and of challenging inoculation. The immunizing antigens consisted of lyophilized spirochetes obtained from rabbit testicular syphilomas, either alone or mixed with falba® or Mycobacterium phlei. Although the injection of these antigens did produce positive reactions to serologic tests for syphilis in rabbits, they failed completely to protect the animal against minimal infectious inoculums of T. pallidum.

Arnold, Mahoney and Cutler[11] describe a further experiment designed to study the immune factors in rabbit syphilis. They employed the Nichols strain of T. pallidum in infecting 34 normal male rabbits, in all of which scrotal chancres developed. These lesions were allowed to heal spontaneously. The animals were then observed for eight months without treatment, after which they were treated with 300 units of sodium penicillin per kilogram every two hours for forty-eight injections, a total of 16,400 units per kilogram, i. e., nearly ten times the already determined curative dose for early rabbit syphilis. Ten days after termination of this therapy the animals were reinoculated intratesticularly with the Nichols strain. In none of the 34 animals did a chancre develop at the site of reinoculation. After four months of clinical observation, the inguinal and popliteal nodes were transferred to normal animals, which were observed for one hundred days. Eighteen of these transfer animals (53 per cent) "developed syphilis," indicating a symptomless reinvasion in the originally inoculated animal. The remaining 16 transfer animals failed to exhibit clinical evidence of syphilis, and subsequent node transfers from this group did not produce any demonstrable syphilitic lesions.

These data are to be compared with an earlier study by the same group of authors[12] (described in the 1947 review), in which rabbits with early syphilis treated with penicillin could be uniformly reinfected if inoculation was carried out ten days after the completion of treatment, i. e., at a time when the original chancre was still present though healing

10. Magnuson, H. J.; Halbert, S. P., and Rosenau, B. J.: Attempted Immunization of Rabbits Against Syphilis with Killed Treponema Pallidum and Adjuvants, J. Ven. Dis. Inform. **28**:267 (Dec.) 1947.

11. Arnold, R. C.; Mahoney, J. F., and Cutler, J. C.: Reinfection in Experimental Syphilis in Rabbits Following Penicillin Therapy: II. Reinfection in Early Latent Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:489 (Sept.) 1947.

12. Arnold, R. C.; Mahoney, J. F., and Cutler, J. C.: Reinfection in Experimental Syphilis in Rabbits Following Penicillin Therapy, Am. J. Syph., Gonor. & Ven. Dis. **31**:264 (May) 1947.

and when the animals were (presumably) still seropositive. The contrast between the earlier and the present study permits the conclusion that the immune factors occurring in early latent syphilis are more forceful than those observed in early infectious syphilis. The potency of the protective reaction varies with the duration of the disease and with the immune response of each animal.

*The Immunologic Relationship of Experimental Syphilis, Yaws and Spontaneous Rabbit Spirochetosis.*—In two previous reports (included in the 1947 review) McLeod and Turner described the general course of experimental (rabbit) syphilis, yaws and spontaneous spirochetosis, the similarity in the rise in serologic titer and the response to antisyphilitic treatment of these three infections. They concluded that T. pallidum, Treponema pertenue and Treponema cuniculi are biologically closely related. Turner, McLeod and Updyke [13] now expand these studies by experiments in cross immunity. In rabbits infected intratesticularly with T. pallidum, T. pertenue or T. cuniculi an appreciable degree of cross immunity to intracutaneous challenge inoculations of each of the same species of spirochetes developed within six months. The immunity to the spirochetes of syphilis produced by infection with T. cuniculi was of a somewhat lesser degree than the resistance produced by T. pallidum to subsequent infection with T. cuniculi, but the differences were not marked.

These studies, of course, confirm the close biologic relationships of the three strains of treponemes. Turner and his associates discuss the question of variation or mutation of species and the possible common origin of the three clinically different infections which they produce. They suggest that effective control, both of syphilis and yaws, may eventually depend on a practical method of artificial immunization and that the potentialities of T. cuniculi as an immunizing agent should be further explored. (It is not yet clear whether cuniculi infection can be produced in man.)

*Experimental Syphilotherapy.*—Utilizing 727 male rabbits, including 80 control animals, Carpenter and Boak [14] evaluated the concurrent treatment of experimental syphilis with fever and oxophenarsine hydrochloride. Five subcurative dosage levels of this drug with fever were evaluated, ranging from 1.0 to 4.0 mg. per kilogram. Effects of fever of three and of five hours' duration used concurrently with the arsenical

13. Turner, T. B.; McLeod, C., and Updyke, E. L.: Cross Immunity in Experimental Syphilis, Yaws, and Venereal Spirochetosis of Rabbits, Am. J. Hyg. **46**:287 (Sept.) 1947.

14. Carpenter, C. M., and Boak, R. A.: Concurrent Treatment of Experimental Syphilis with Fever and Mapharsen, Am. J. Syph., Gonor. & Ven. Dis. **31**:498 (Sept.) 1947.

were compared at 41.1 C. and 41.5 C. Groups of infected rabbits were treated with oxophenarsine hydrochloride only or with fever only to serve as controls for the subcurative doses of the two agents employed concurrently. Whereas Eagle reported the curative dose of this arsenical when used alone in experimental syphilis to be approximately 7.0 mg. per kilogram of body weight, in the present study as little as 1.5 mg. per kilogram along with fever therapy cured from 83 to 91 per cent of the rabbits and 3.0 mg. per kilogram with fever therapy cured from 95 to 100 per cent. Neither duration of fever, degree of temperature nor time of administration of oxophenarsine hydrochloride prior to or at the termination of fever significantly influenced the therapeutic result.

A discussion of the action of penicillin on T. pallidum based on a review of the literature is presented by Beerman.[15] Sixty-two references are cited. This article does not lend itself to abstraction and should be consulted in the original.

Arnold and others[16] report a collaborative investigation undertaken to determine the relative efficacy of various species of penicillin in the treatment of experimental rabbit syphilis. A uniform approach to the problem was agreed on, the details of which are presented. Each investigator treated six groups of 10 rabbits each with a given specimen of a penicillin species. Treated animals were observed for one hundred and twenty days after treatment, at the end of which time lymph node transfers were made to normal rabbits. All the latter rabbits were kept four months before being classified as free from the disease. Penicillin G was the most potent of the penicillins used ($CD_{50}$ 1,000 to 2,000 units per kilogram) and F about one sixth as effective ($CD_{50}$ 5,200 to 20,800 units per kilogram). The highest dose of penicillin K tested, 16,000 units per kilogram, failed to cure half the animals treated. The data on penicillin X were inexplicably discrepant.

The evaluation of the therapeutic efficacy of chemotherapeutic compounds, in a disease so insidious and chronic as syphilis, is at present a prolonged and expensive undertaking. In experimental rabbit syphilis, the standard technic does not allow a conclusion in less than eleven months, since it has always been thought necessary to carry out lymph node transfers in order to be certain that rabbits have actually been cured. Two different technics have been recently suggested to enable the investigator to obtain conclusions in a shorter period.

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15. Beerman, H.: The Action of Penicillin on Treponema Pallidum, Am. J. M. Sc. **214**:442 (Oct.) 1947.

16. Arnold, R. C.; Boak, R. A.; Carpenter, C. M.; Chesney, A. M.; Fleming, W. L.; Gueft, B.; Mahoney, J. F., and Rosahn, P. D.: A Joint Report on a Cooperative Investigation of the Efficacy of Species of Penicillin in the Treatment of Experimental Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:469 (Sept.) 1947.

Rake, Dunham and Donovick [17] have studied the prophylactic effect of various antibiotics (mostly penicillins) in experimental rabbit syphilis. A measured inoculum of T. pallidum is injected intradermally (producing syphilomas in all control animals). Six hours after inoculation treatment is begun, and its success or failure is measured by the appearance or nonappearance of dark field–positive syphilitic lesions. The adequacy of this standard of efficacy has been measured in a large series of animals by lymph node transfer, which altered the clinical conclusions in only 4 per cent. In these circumstances, the authors feel that lymph node transfer as a criterion of prophylactic effect can be eliminated and a valid answer in regard to the relative efficacy of treponemicidal compounds determined within ten weeks. Utilizing this abbreviated technic, the authors found the $PD_{50}$ (the prophylactic dose protecting 50 per cent of the animals) for crystalline penicillin G to be 109 units, for penicillin X 173 units, for penicillin K 645 units, and for mixtures of penicillin F and dihydro F between 170 and 310 units per kilogram. In confirmation of earlier studies from their own and other laboratories, certain impure penicillin samples were more active than crystalline G. The $PD_{50}$ of streptomycin was 135,000 units per kilogram, and the effect of penicillin and streptomycin in combination was only additive and not synergistic. It is to be noted that the $PD_{50}$ by this technic is in all cases much less than the $CD_{50}$ of the same compounds (about one tenth to one twentieth) when tested in established early infections and that the method provides relative results only.

Turner, Cumberland and Li [18] also report a still shorter (twenty-four hour) method for testing the relative therapeutic activities of various penicillins in rabbits experimentally infected with T. pallidum. Syphilomas were produced on the backs of rabbits by intradermal inoculation. Penicillin was then given intramuscularly in three equal doses at two hour intervals. When effective doses were employed, spirochete counts averaging about 1,000 treponemes per 200 dark fields before treatment fell to 10 or less in twenty-four hours. When this method was employed the $ED_{50}$ (effective dose in one-half the animals) for several crystalline penicillins was as follows (in milligrams per kilogram): G, 0.11; F, 0.63; K, more than 2, and X, 1.2. Expressed in Oxford units per kilogram, the comparative values were

17. Rake, C.; Dunham, W. B., and Donovick, R.: The Evaluation of Antibiotics by the Prevention of Experimental Syphilis, J. Infect. Dis. **81**:122 (Sept.-Oct.) 1947.

18. Turner, T. B.; Cumberland, M. C., and Li, H. Y.: Comparative Effectiveness of Penicillin G, F, K and X in Experimental Syphilis as Determined by a Short in Vivo Method, Am. J. Syph., Gonor. & Ven. Dis. **31**:476 (Sept.) 1947.

as follows: G, 183; F, 1,024; K, more than 4,380, and X, 1,053. After the administration of amounts of penicillin at or above the $ED_{50}$ level, disappearance of T. pallidum from syphilomas was rapid. Significant decreases in numbers of spirochetes were noted in four to six hours, and commonly 99 per cent had disappeared twenty-four hours after the initial dose of penicillin.

Eagle and Fleischman [19] have also studied the relative antisyphilitic activities of various antibiotic preparations by a short method involving the abortion of syphilitic infection in rabbits. Animals inoculated intradermally with a measured inoculum of 2,000 T. pallida organisms were treated four days later with intramuscular injections of the various penicillins or with bacitracin, repeated once daily for fourteen days. The doses of penicillins F, G, K and X and of bacitracin which aborted infection in half the animals were respectively 3.5, 0.3, 2.6 and 2.2 mg. per kilogram and 90 units per kilogram. Penicillins F, K and X were therefore 8, 12 and 14 per cent as active per milligram as penicillin G; a crude preparation of bacitracin assayed at 30 units per milligram was 10 per cent as active as penicillin G.

Figure 1 is taken from Eagle and Fleischman's article showing the relative activities of these several preparations against T. pallidum by five different methods of assay and comparing their own results with those reported in the two papers just cited. According to the authors, "It is apparent that not only the absolute but also the relative antisyphilitic activity of the several penicillins and of bacitracin varies widely according to the method of assay." When the figure is carefully studied, however, it appears that in vivo methods (the lower four graphs) correspond at least relatively in satisfactory fashion; the single in vitro method listed (the upper graph of the figure) is at wide variance. It appears, therefore, that in vitro methods of assay are not satisfactory, even in a relative sense.

On the whole, it seems to the reviewers that since all methods of evaluating penicillin in rabbit syphilis yield data which are only roughly applicable to the therapeutic activity of these drugs in human syphilis, short methods of assay such as these are probably as capable of satisfactory measures of the relative value of chemotherapeutic compounds as earlier and more prolonged evaluation of cure.

Two reports have appeared concerning the use of penicillin in peanut oil-beeswax [20] in experimental rabbit syphilis. Fleming and

19. Eagle, H., and Fleischman, R.: The Relative Antisyphilitic Activity of Penicillins F, G, K and X and of Bacitracin, Based on the Amounts Required to Abort Early Syphilitic Infections in Rabbits, J. Bact. **55**:341 (March) 1948.

20. Hereafter abbreviated to POB, editorial comment "More Silly Names for Penicillin Products" (J. A. M. A. **137**:1043 [July 17] 1948) to the contrary notwithstanding.

Holcombe [21] studied the effectiveness of POB when administered in sixteen daily injections to rabbits with early syphilis. The penicillin concentrations of the suspensions used were necessarily lower than that of the Romansky formula, in order to permit accurate estimation of small doses. With a total dosage of 250 to 500 units per kilogram,

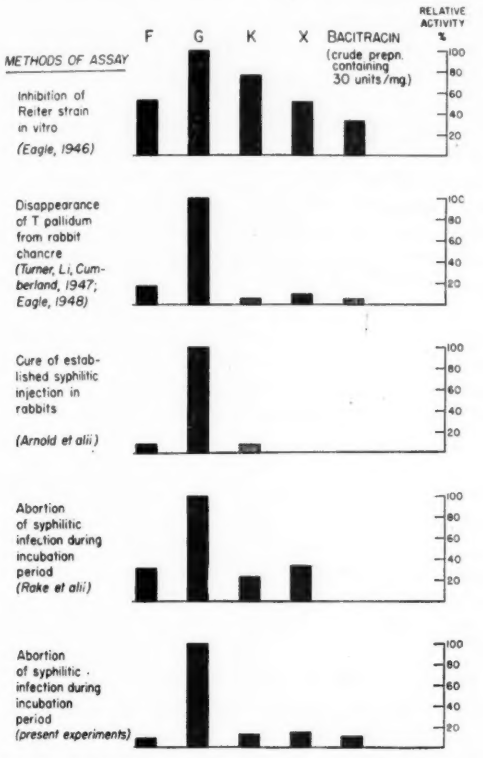


Fig. 1.—The relative activity of penicillins F, G, K and X and of bacitracin against T. pallidum by five different methods of assay. Cross-hatched blocks are results which are approximations only. (Eagle, H., and Fleischman, R.: J. Bact. **55**:341 [March] 1948.)

all of 19 rabbits failed to be cured; with 1,000 units per kilogram only 1 of 8 rabbits failed to be cured. With dosages of 4,000 to 16,000

21. Fleming, W. L., and Holcombe, M. W.: The Effectiveness in Experimental Syphilis of Penicillin in Peanut Oil-Beeswax Given in Sixteen Daily Injections, Am. J. Syph., Gonor. & Ven. Dis. **32**:53 (Jan.) 1948.

units per kilogram, there were no failures among 28 rabbits treated. Thus the $CD_{50}$ was 1,400 units per kilogram when calculated according to the Reed-Muench formula. This is approximately the same $CD_{50}$ as had been obtained by Eagle and independently by Fleming with injections of aqueous solutions of commercial penicillin or of crystalline G given every three to four hours over a four day period. In early rabbit syphilis, the $CD_{50}$ of sixteen single daily injections of aqueous penicillin has been reported by Eagle to be 4,000 units per kilogram (as compared with 1,400 units per kilogram for POB) given on an identical schedule.

Rosahn and Gueft [22] made a similar study of the therapeutic efficacy of (calcium) POB administered intramuscularly in eight equal daily injections in the treatment of experimental rabbit syphilis. Treatment was begun six weeks after the intratesticular inoculation of these rabbits with the Nichols strain of T. pallidum. Total dosage ranged from 250 to 16,000 units per kilogram. A $CD_{50}$ of 1,070 units per kilogram of body weight was observed. This value does not differ significantly from the $CD_{50}$ of 1,400 units per kilogram reported by Fleming after administration of a similar preparation in sixteen equal daily doses. Therefore, when POB is employed in the treatment of rabbit syphilis, increasing the number of daily injections from eight to sixteen does not alter the total curative dose.

Penicillin in peanut oil-beeswax is rapidly being replaced commercially by the highly insoluble (in water) procaine penicillin G suspended in oil (peanut or sesame) with or without the addition of 2 per cent aluminum monostearate. Since the bacterial spectrum of procaine penicillin appears to be identical with that of the sodium or calcium salts, and since detectable blood levels persist for even longer periods after injection of comparable doses of the procaine salt than after injection of the oil-beeswax mixtures, it is reasonable to assume that the data furnished for POB, in regard to both experimental animals and man, will hold good for procaine penicillin as well; perhaps, even, the results may be improved on (see further comment on procaine penicillin).

Kolmer [23] has estimated the therapeutic activity of oral penicillin in the treatment of experimental syphilis of rabbits. Three rabbits were employed for each of the following individual doses: 500, 1,000, 5,000, 10,000, 15,000 and 20,000 units per kilogram of body weight.

22. Rosahn, P. D., and Gueft, B.: Therapeutic Efficacy in Experimental Syphilis of Eight Daily Injections of Penicillin in Beeswax-Peanut Oil, Proc. Soc. Exper. Biol. & Med. **66**:402 (Nov.) 1947.

23. Kolmer, J. A.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: III. The Therapeutic Activity of Penicillin by Oral Administration, Arch. Dermat. & Syph. **56**:344 (Sept.) 1947.

Sixteen rabbits were given thirty doses, 1 twenty-one doses and another forty-two doses. Dark field examinations were carried out at intervals up to forty-nine days. Small doses of penicillin by mouth, such as 500 units per kilogram three times a day for a total of thirty doses (15,000 units), may result in temporarily negative reactions to dark field examinations. On the basis of lymph node transfers, the minimal curative dose in the treatment of acute syphilitic orchitis of rabbits is 15,000 to 20,000 units per kilogram given three times a day for thirty doses, a total of 450,000 to 600,000 units. This dose in the rabbit would correspond to a total dose of 30,000,000 to 50,000,000 units in the treatment of early syphilis of the human adult, provided the total dose required for biologic cure of the latter were the same as that required for the cure of acute syphilis of rabbits. However, since for "cure" man requires, on the average, five times as much penicillin as does the rabbit, Kolmer agrees that oral penicillin therapy in the treatment of syphilis in man is undesirable unless, perhaps, it is combined with the administration of oxophenarsine hydrochloride or bismuth.

Magnuson and Rosenau [24] compare penicillin alone with penicillin plus bismuth in the treatment of experimental rabbit syphilis. With amorphous sodium penicillin, containing 35 per cent penicillin G, 35 per cent penicillin K and 30 per cent penicillin F, given five times daily for four days, the $CD_{50}$ was 2,650 units per kilogram and the $CD_{90}$ 8,000 units. The addition of one fourth of the $CD_{50}$ of bismuth subsalicylate (1.2 mg. of bismuth per kilogram) to this schedule reduced the $CD_{50}$ of penicillin to 1,000 units per kilogram when bismuth was given at the start of penicillin therapy and to 1,500 units when it was given at the end. The $CD_{90}$ values were reduced to 1,800 units per kilogram and 3,300 units per kilogram respectively. The addition of one fourth of the $CD_{50}$ of bismuth potassium tartrate (1.1 mg. of bismuth per kilogram) to the penicillin schedule reduced the $CD_{50}$ of penicillin to 500 units per kilogram and the $CD_{90}$ to 1,800 units. The addition of three fourths of the $CD_{50}$ of bismuth subsalicylate (4.2 mg. of bismuth per kilogram) either at the beginning or at the end of penicillin therapy reduced the $CD_{50}$ of penicillin to 110 units per kilogram and the $CD_{90}$ to 250 units. It is concluded that bismuth and penicillin are as synergistic in the treatment of early rabbit syphilis as are oxophenarsine hydrochloride and penicillin. As is later indicated, however, this apparent synergism does not apply equally in man.

*Bacitracin and Subtilin in the Treatment of Syphilis.*—The action of bacitracin and subtilin on T. pallidum in vitro and in vivo is re-

24. Magnuson, H. J., and Rosenau, B. J.: Bismuth Plus Penicillin in the Treatment of Experimental Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **32**:203 (May) 1948.

ported by Eagle, Musselman and Fleischman.[25] Most of the paper is taken up with comparative in vitro studies, doubt as to the relative validity of which has been provided from Eagle's own laboratory.[19] In experimental animals 1 mg. of penicillin was as effective as were 300 units of bacitracin in the abortion of syphilitic infection. By this method of assay, penicillin was therefore ten times as effective as a crude preparation of bacitracin in doses of 30 units per kilogram. Subtilin, which showed some treponemicidal activity in vitro (though penicillin G similarly tested was sixty-four to one hundred and twenty-eight times as effective), had no obvious effect when given to 4 rabbits with testicular chancres in a dosage of 10 mg. per kilogram four times daily for four days. Apparently it has little or no value against this organism.

*Local Prophylaxis of Syphilis with Arsenic.*—Arnold and Mahoney [26] have pursued further the earlier demonstration by Eagle, Magnuson and Fleischman (see 1947 review) that phenyl arsenoxide in ointments and soap was effective in local prophylaxis against syphilis. Pledgets of cotton soaked in a suspension of virulent T. pallidum were inserted into the preputial sac of male rabbits and retained in place for one to two hours, with frequent remoistening with spirochete suspension. The inoculation thus produced through the intact mucosa (all animals with macroscopic evidence of mucosal trauma were discarded) was assumed to be analogous to the natural mode of inoculation in man. In all control animals (exact number not stated but presumably, from evidence in the paper, about 35) there developed dark field–positive lesions of syphilis. After one to two hours of such exposure, 27 animals were given prophylactic treatment with an aqueous solution of oxophenarsine hydrochloride ("mapharsen") in concentrations of 0.025 and 0.1 per cent. Of these, syphilis developed in 5, and 22 were protected. Since "mapharsen" in water is unstable and lacks the cleansing properties and the psychologic effect of soap, mixtures of the arsenical and various detergents (which have cleansing and "sudsing" properties) were tried. Alkyl aryl sulfate (concentration 1.0 to 2.0 per cent) was found to be suitable for mixture with "mapharsen" (concentration, 0.1 to 0.2 per cent), though data are not provided on the stability of the mixture. One hundred and fifty-seven rabbits were treated prophylactically with this mixture after one to two hours of exposure; syphilis developed in 3, and 154 were protected. It is understood that a field trial of this form of chemical prophylaxis is under

25. Eagle, H.; Musselman, A. D., and Fleischman, R.: The Action of Bacitracin and Subtilin on Treponema Pallidum in Vitro and in Vivo, J. Bact. **55**:374 (March) 1948.

26. Arnold, R. C., and Mahoney, J. F.: Local Prophylaxis in Experimental Syphilis of the Rabbit, J. Ven. Dis. Inform. **29**:138 (May) 1948.

way in the United States Army, the results of which are not yet available.

*Experimental Mouse Syphilis.*—Gueft and Rosahn [27] present a critical review of the literature concerning experimental mouse syphilis, summarizing in detail the literature of the past forty years and culling from it the known facts and the controversial issues. This extensive review is not susceptible of presentation in abstract form, and the original article should be consulted by those interested.

Johnson and Wile [28] pursue further the possibility of an infectious granular form of T. pallidum. They report a series of experiments demonstrating that infected mouse organs capable of causing syphilitic orchitis in rabbits lost this capacity after filtration through a coarse Mandler diatomaceous filter. On the other hand, the filtrates of dark field–positive rabbit testicular material were infectious for normal rabbits, though this effect was lost when rabbit testis was mixed with mouse brain. The inability of filtrates of syphilitic mouse brains and organs to cause orchitic changes in rabbits does not entirely eliminate a filtrable infravisible form of T. pallidum as the infectious agent in mice. It is suggested that there may be a colloidal action of mouse tissue which affects the filtrability of spiral forms of the organism.

### SERODIAGNOSIS

*Quantitative Serologic Tests.*—Taggart [29] discusses for the practitioner the use of quantitative serologic tests for syphilis. Similar discussions are given by Scott and Clark [30] and, in abbreviated form, by Kuehn and Damon.[31]

*Biologic False Positive Reactions, Clinical Aspects.*—Nelson [32] tested the serums of 200 nonsyphilitic patients under treatment for

27. Gueft, B., and Rosahn, P. D.: Experimental Mouse Syphilis: A Critical Review of the Literature, Am. J. Syph., Gonor. & Ven. Dis. **32**:59 (Jan.) 1948.

28. Johnson, S. A. M., and Wile, U. J.: The Use of the Mandler Diatomaceous Filter in the Study of the Infectious Agent in Syphilitic Mice, Am. J. Syph., Gonor. & Ven. Dis. **31**:493 (Sept.) 1947.

29. Taggart, S. R.: A Discussion of the Clinical Application of Titered or Quantitative Serologic Tests for Syphilis, M. Ann. District of Columbia **17**:135 (March) 1948.

30. Scott, V., and Clark, E. G.: Quantitative Serologic Tests for Syphilis: Use and Availability in Venereal Disease Control, South. M. J. **40**:685 (Aug.) 1947.

31. Kuehn, C. C., and Damon, S. R.: Quantitative Serology and Syphilis: I. Meaning of Qualitative and Quantitative Tests, J. Indiana M. A. **41**:318 (March) 1948; II. The Role of Quantitative Serologic Tests in the Diagnosis of Syphilis, ibid. **41**:424 (April) 1948; III. Serologic Follow-Up on Patients Treated for Syphilis by a Short Intensive Method, ibid. **41**:513 (May) 1948.

32. Nelson, M. G.: Serologic Tests for Syphilis in Treated Plasmodium Falciparum Malaria, Tr. Roy. Soc. Trop. Med. & Hyg. **41**:127 (Sept.) 1947.

Plasmodium falciparum malaria with the Ide, Kahn and Meinicke flocculation tests. In about 3 per cent biologic false positive reactions were noted. These persisted for two months or less. The incidence of false positive reactions noted is far below that demonstrated by many other workers in the more extensively studied Plasmodium vivax malaria.

Fleming and Heffner [33] suggest that the positive reaction to the blood serologic test in so many cases (over 90 per cent) of paroxysmal cold hemoglobinuria may be, in some at least, a biologic false positive reaction. This suggestion is based on the twin facts that in many cases of paroxysmal hemoglobinuria the only evidence of syphilis is serologic and that in some the hemoglobinuric tendency persists after antisyphilitic treatment. (Many cases of cure of the condition have been reported.)

Gasser [34] reviews the histories of 50 children who had pneumonia of the virus type and positive serologic reactions to tests for syphilis. He believes that a constitutional factor may be present in biologic false seropositivity, since many of the children were from families in which allergy was present, were susceptible to catarrhal infection and had nutritional disturbances. However, even though 2 children of the same family might have the same type of pneumonic infiltration of the lungs, both did not necessarily have positive serologic reactions to tests for syphilis. Reactions to tests for cold agglutinins were rarely positive. There was an increase in serum globulin in children having false positive serologic reactions.

Seeking an answer to the question of whether there is such an entity as persistently positive, familial, nonspecific reactions to a serodiagnostic test for syphilis, Singer and Boerner [35] have studied, over a period of two years, 6 members of an Italian family. Of the 6, 4 had persistently positive reactions to flocculation tests together with negative reactions to complement fixation tests, although there was no anamnestic or clinical evidence of syphilis in any of them. A study of the blood groups indicated that the mother and 3 children (those who had positive reactions to flocculation tests) all had blood of type A whereas the father and 1 child, who reacted negatively to serologic tests, had

33. Fleming, G. G., and Heffner, B. L.: Paroxysmal Cold Hemoglobinuria: Report of Two Cases, North Carolina M. J. **9**:142 (March) 1948.

34. Gasser, C.: Wassermann-Positive Bronchopneumonia During Childhood and Its Various Manifestations (Fanconi-Hegglin's Syndrome): Contribution to Aspects of Miliary Bronchopneumonia and Virus Pneumonia, Helvet. paediat. acta **2**:185 (June) 1947.

35. Singer, A. G., Jr., and Boerner, F.: Persistent Familial (Non-Specific) Serologic Flocculation Reactions for Syphilis Suggesting an Hereditary Mechanism, Am. J. M. Sc. **214**:89 (July) 1947.

blood of type O. This suggested to these workers that a hereditary mechanism may have been responsible for the existence of the observed serologic phenomena.

*The Laboratory Differentiation of Biologic False Positive Serologic Reactions.*—For nearly forty years serologists have attempted to develop technics which might serve to differentiate the positive complement fixation or flocculation reactions occurring in cases of syphilis and other spirochetal infections from the biologic false positive reactions (subsequently abbreviated BFP) occurring naturally in normal nonsyphilitic persons or induced in them by various extraneous influences. These efforts have led to a host of "presumptive," "exclusion" or "verification" tests which, as many of the earlier reviews of this series have indicated, have never successfully presumed, excluded or verified anything. The fundamental difficulty appears to be that current serologic tests for syphilis are crude tools which measure a purely nonspecific antibody ("reagin"), uniformly produced by spirochetal infections but often by other influences as well, by means of a wholly nonspecific (beef heart lipid) antigen, purified to greater or lesser degree (see discussion of cardiolipin antigen, page 97). If, in syphilis, specific antibodies are elaborated against the invading organism, T. pallidum, as is almost certainly the case, these cannot be serologically estimated for lack of a pure antigen derived from cultured virulent treponemes, which have never been successfully grown on artificial mediums. Moreover, practically all efforts to date have depended on "serologic cookbookery," the juggling of reagents to adjust specificity against sensitivity.

The mass blood testing of many millions of the American population which preceded, accompanied and follows World War II has reemphasized and sharpened the magnitude of the BFP problem. Thousands of persons, in whom there is no clinical reason to suspect syphilitic infection or even exposure to it, are found annually to have seropositive reactions. The situation has become so acute that clinicians frequently (and often properly) refuse to accept serologic evidence of syphilis unless supported by other data and so serious as to cast doubt on the desirability of continuing compulsory blood testing laws (e.g., premarital).

Stimulated by the importance of this diagnostic problem, Neurath and his associates at Duke University have undertaken a new study, based, for the first time, on immunochemical methods, in an effort to determine whether "reagin" produced in syphilis is qualitatively or only quantitatively different from the "reagin" occurring in certain normal persons or produced in them by extraneous factors. Their preliminary experimental studies have been presented in a series of

six papers[36]; and though a test suitable for practical and general application has not yet been worked out, the method ("euglobulin-inhibition") is sufficiently promising to warrant much further work.

This group of papers is highly technical and details the various preliminary steps necessary prior to development of the technic now in use. They are here reviewed as a group and in simplified form. The student interested in experimental minutiae must consult the original.

The first effort was to determine with which component of human serum reagin is associated. With the use of both electrophoretic and chemical methods of fractionation, it was found (as had already been determined by others) that serologic reactivity resided in the globulin fractions, serum albumin being devoid of reagin. Most of the reactivity was in the gamma GI and GII (euglobulin) fractions; a little was in the GIII fractions. This was true both of serums derived from known syphilitic patients and of those from persons with proved BFP reactions. Tests for the presence of reagin in both parent serum and protein fractions have of necessity been carried out with standard beef heart lipid antigens, of which the most satisfactory have been found to be the Mazzini and cardiolipin antigens.

By appropriate methods of chemical fractionation of serums, a large amount of serologically inert serum protein is eliminated and a seven-

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36. (*a*) Neurath, H.; Volkin, E.; Erickson, J. O.; Craig, H. W.; Putnam, F. W., and Cooper, G. R.: Biologic False Positive Reactions in Serologic Tests for Syphilis: I. Preparation and Properties of Serologically Active Serum Globulin Fractions Obtained by Fractional Precipitation with Ammonium Sulfate, Am. J. Syph., Gonor. & Ven. Dis. **31**:347 (July) 1947. (*b*) Erickson, J. O.; Volkin, E.; Craig, H. W.; Cooper, G. R., and Neurath, H.: Biologic False Positive Reactions in Serologic Tests for Syphilis: II. Preparation and Properties of Serologically Active Serum Euglobulin Fractions Obtained by Isoelectric Precipitation, ibid. **31**:374 (July) 1947. (*c*) Volkin, E.; Neurath, H.; Erickson, J. O., and Craig, H. W.: Biologic False Positive Reactions in Serologic Tests for Syphilis: III. Preparation and Properties of Serum Protein Fractions Which Inhibit Biologic False Positive Reactions, ibid. **31**:397 (July) 1947. (*d*) Volkin, E.; Neurath, H., and Craig, H. W.: Biologic False Positive Reactions in Serologic Tests for Syphilis: IV. Quantitative Aspects of the Inhibition Phenomenon, ibid. **31**:413 (July) 1947. (*e*) Neurath, H.; Volkin, E.; Craig, H. W., and Erickson, J. O.: Biologic False Positive Reactions in Serologic Tests for Syphilis: V. A. Preliminary Survey Analysis with the Euglobulin-Inhibition Method for the Serologic Differentiation Between True and Biologic False Positive Reactions, ibid. **31**:436 (July) 1947. (*f*) Putnam, F. W.; Volkin, E.; Craig, H. W., and Neurath, H.: Biologic False Positive Reactions in Serologic Tests for Syphilis: VI. Partial Purification of the Antibodies of Syphilitic Human Sera by Absorption on Freshly Precipitated Calcium Phosphate, ibid. **31**:457 (July) 1947.

fold or greater concentration of reagin accomplished in the euglobulin fraction.

Whether by electrophoretic or by chemical methods of fractionation, there was no significant difference in the component protein fractions of human serums derived from normal or syphilitic persons and of those from persons with BFP reactions. However, an important point, developed early, proved to be the quantitative serologic titer of globulin fractions related to the titer of the parent serum. In syphilitic human serums the sum total of the serologic titers observed in the globulin fractions was usually less than, or at best equal to, that of the parent serum. In BFP serums, on the other hand, the total of the titer in the globulin fractions was usually higher than that in the parent serum and in a number of cases in which this occurred serologic reactivity, sometimes of high titer, was present in the euglobulin fraction even though serologic tests of the parent serum gave negative reactions. Control experiments on fractions derived from normal serum gave entirely negative results.

This differential serologic behavior of syphilitic versus BFP serums, while throwing no light on a possible qualitative difference in the antibodies (reagin) elaborated in the two sets of circumstances, did, however, suggest the hypothesis that in certain serums some substance inhibiting flocculation with beef heart lipid antigen might have been eliminated in the process of fractionation. Experiments undertaken to test this hypothesis showed that more than half of normal, syphilitic or BFP serums did contain in their crude, serologically inert albumin fractions (which also included a small amount of globulin) a selectively active inhibiting factor. The selective inhibitor was not present in crystalline serum albumin but was found to be present in fractions IV-1 and III-0 in pools of human plasma, greater in concentration in the former. The inhibitory factor, studied by various immunochemical methods, has not been definitely identified, but it is suggested that it may be a lipoprotein.

Experiments were now undertaken to investigate the quantitative aspects of the inhibition phenomenon and to clarify its mechanism. Within a wide range of inhibitor concentration, inhibition was selectively directed toward the flocculation reaction of the biologic false positive type, that of the syphilitic type being hardly affected. The inhibition phenomenon was more specific toward antigens of high chemical purity such as cardiolipin than toward less purified beef heart lipid antigens. The extent of inhibition of the biologic false positive reaction was dependent on the amount of antigen and inhibitor present in the system but was apparently independent of antibody titer. A minimal ratio of inhibitor antigen was required for complete inhibition. Below that ratio and over a limited range inhibition was a linear function of the

logarithm of that ratio, whereas a several-fold increase of the threshold ratio resulted in gradual inhibition of the syphilitic type of reaction as well.

As an explanation of the mechanism of inhibition of the BFP reaction, it was proposed that in a system containing all three reactants, that is, antigen, antibody and inhibitor, the competition for the antigen occurred between antibody and inhibitor. Since true reactions and BFP flocculation reactions differ from each other only in the types of antibodies involved, the other two reactants being the same, it was suggested that in a BFP reaction the inhibitor reacts with the antigen in preference to the antibody whereas in the true syphilitic type of reaction the antibodies react preferentially with the antigen. In other words, the affinity of true syphilitic antibody for antigen is greater than is the affinity of inhibitor for antigen, but the affinity of BFP antibody for antigen is less than the affinity of inhibitor for antigen. Since the antigen-inhibitor complex is soluble, no flocculation occurs in the latter circumstance.

On the basis of these observations, the procedure for the serologic differentiation between true and BFP reactions at present consists in (1) preparation of a serologically active serum euglobulin fraction by the method of isoelectric precipitation, (2) addition of the heat-stable serum inhibitor to a split sample of the euglobulin solution and (3) quantitative comparison of the serologic titer of the euglobulin solution with that of the euglobulin-inhibitor mixture. Quantitative serologic titrations are carried out on three solutions: (1) whole serum, (2) euglobulin solution and (3) euglobulin-inhibitor mixture. The inhibition reaction is considered to be of the BFP type if the euglobulin solution is serologically positive and the euglobulin-inhibitor mixture entirely negative. Comparable ranges of titer of the euglobulin solution and of the euglobulin-inhibitor mixture are indicative of a syphilitic type of reaction. Even under optimal conditions of performance the inhibition test may yield inconclusive results. These have been noted when the initial titer of the euglobulin fraction was of low magnitude, that is, 1 to 1.5 units.

The euglobulin-inhibition test gave the following results with known BFP human serums: Of 129 samples of seropositive malaria blood, 93 per cent showed the BFP type of reaction; of 53 patients with seropositive reactions who had infection of the upper respiratory tract, 89 per cent had the BFP type of reaction; of 65 patients thought to have false positive reactions of unknown cause, 97 per cent had the BFP type of reaction, and of 9 samples of blood from patients with leprosy, 100 per cent showed the BFP type of reaction. This distribution was independent of serologic titer of the euglobulin fraction.

Of 386 serums from patients with clinically proved syphilis, other than low-titered serums from untreated patients with early primary syphilis, 327 had serologically-positive euglobulin fractions. Of these, 95 per cent gave a syphilitic type of inhibition reaction and only 2 per cent a biologic false positive type of inhibition reaction. This distribution was also independent of serologic titer of the euglobulin fraction and of antisyphilitic therapy. Low-titered serums from untreated patients with early primary syphilis gave a high incidence of BFP inhibition reactions. This may be ascribed to the presence of syphilitic antibodies of altered serologic specificity; or it may be assumed that in the early stages of disease, before specific antibodies have developed, those reactive antibodies that may be detected are specifically unrelated to disease and hence are actually of the BFP type.

Of 95 presumably syphilitic human serums with serologically positive globulin fractions, 88 per cent gave a syphilitic type of inhibition reaction. Of 50 serums from patients with pinta, 96 per cent gave a syphilitic type of inhibition reaction, as did also all of 9 serums from patients with yaws. The percentage distribution between syphilitic and biologic false positive reactions in a group of serums of originally undisclosed diagnostic origin was comparable to that found in the entire series of known biologic false positive and syphilitic human serums.

Further work on this technically complicated procedure is proceeding in a cooperative effort of four laboratories. It has not yet been shown that the results of the Duke investigators are standardizably repeatable in other laboratories. The technic, which has been constantly changing during the several years of experimental study, may change still further as additional information develops. Especially desirable of clarification are the yet unsolved problems of possible qualitative immunochemical differences between antibodies of syphilitic and BFP origin and the nature of the inhibitor. The test is far from ready for general application or for absolute clinical acceptance; but it certainly holds more promise than any of the misnamed "verification" tests so far developed.

*Cardiolipin Antigen in the Serodiagnosis of Syphilis.*—Pending the successful cultivation of T. pallidum on artificial mediums and the development therefrom of an antigen wholly specific for the antibodies produced by this organism, two avenues of approach to the development of greater specificity of serologic tests have been obvious. One, exemplified by the work of Neurath and his collaborators, has attempted to differentiate by immunochemical methods (using standard nonspecific tissue extract antigens for serologic testing) between the antibodies produced in syphilis and those produced in other conditions. The other, exemplified by many serologists beginning with Wassermann himself,

has tried to purify the tissue extract antigens themselves and to determine which component of their exceedingly complex chemical make-up carries with it the greatest serologic reactivity.

The most successful of the latter efforts has been the development, during the past six years, of cardiolipin antigen by Pangborn.[37] Some of the articles dealing with this antigen and its practical application have been noted in previous reviews of this series.

Cardiolipin is probably a pure chemical entity (a complex phosphatidic acid) derived, by elaborate technical methods, from an alcoholic extract of beef heart. When used as an antigen in serodiagnosis, its sensitivity and specificity are enhanced by the addition of purified lecithin and, in some technics, cholesterol. The chemical purity of these three substances and the quantities in which they are concentrated in the final antigen influence both specificity and sensitivity, and, as with other cruder beef heart antigens, these two factors may be adjusted upward or downward by varying the final quantities of the reagents involved. The past year has seen a growing appreciation of this point and several efforts to determine the optimum concentration of the three ingredients. Moreover, it begins to appear that the relative optimal concentrations of cardiolipin, lecithin and cholesterol may vary, depending on whether the serologic technic to be employed is complement fixation, macroflocculation (tube) or microflocculation (slide) tests and on whether the specimen to be tested is blood serum or spinal fluid.

For example, after examining 39 different combinations of cardiolipin, lecithin and cholesterol. Kolmer and Lynch [38] concluded that with the particular Kolmer complement-fixation technic and for blood serum and spinal fluid alike an antigen containing 0.03 per cent cardiolipin, 0.05 per cent lecithin and 0.6 per cent cholesterol is optimal.

Also utilizing the Kolmer complement fixation technic, Kent, Boyd and Sanders [39] decide, on the contrary, that the most satisfactory antigen should contain 0.0175 per cent cardiolipin, 0.0875 per cent lecithin and 0.3 per cent cholesterol.

In flocculation technics, cardiolipin and lecithin have been used sometimes with and sometimes without cholesterol. Here the proportion of cardiolipin to lecithin varies, in different technics, being from 1 : 6.5 to 1 : 25 and usually about 1 : 10.

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37. Pangborn, M. C.: A New Serologically Active Phospholipid from Beef Heart, Proc. Soc. Exper. Biol. & Med. **48**:484 (Nov.) 1941.

38. Kolmer, J. A., and Lynch, E. R.: Cardiolipin Antigens in the Kolmer Complement Fixation Test for Syphilis, J. Ven. Dis. Inform. **29**:166 (June) 1948.

39. Kent, J. F.; Boyd, H. M., and Sanders, R. W.: Cardiolipin Antigen in the Kolmer Complement-Fixation Tests for Syphilis, Bull. U. S. Army M. Dept. **8**:284 (April) 1948.

During the past year, a number of articles dealing with cardiolipin have appeared, notably from Harris and Mahoney,[40] Harris, Rosenberg and Del Vecchio,[41] Vogelsang,[42] Kline,[43] Giordano, Culbertson and Higgenbotham,[44] Andujar, Anderson and Mazurek,[45] Levine, Kline and Suessenguth,[46] Widelock,[47] Kolmer and Lynch,[38] Kent, Boyd and Sanders,[39] Bohls and Shaw,[48] Rein and Coren [49] and Brown.[50]

As to specificity, it is generally agreed that cardiolipin is superior to standard beef heart lipid antigens, especially in malaria. Table 1, modified from the paper of Levine and his associates,[46] indicates that a

TABLE 1.—*False Positive Serologic Reactions in Malaria (from Levine, Kline and Suessenguth)* [46]

| Cardiolipin Antigen | Standard Serologic Technics (Eagle, Hinton, Kahn, Kline, Mazzini) |
|---|---|
| 1 per cent | 8 to 24 per cent |

cardiolipin flocculation test yields almost no false positive results in this condition, whereas random (not serially performed) tests with other antigens elicited positive reactions in from 8 to 24 per cent of specimens tested. This is in confirmation of the previously recorded observations of Rein and Kent (1947 review). Table 2, also modified from the

40. Harris, A., and Mahoney, J. F.: Cardiolipin and Purified Lecithin as Reagents in Syphilis Serology, Am. J. Pub. Health **37**:997 (Aug.) 1947.

41. Harris, A.; Rosenberg, A. A., and Del Vecchio, E. R.: The VDRL Slide Flocculation Test for Syphilis: II. A Supplementary Report, J. Ven. Dis. Inform. **29**:72 (March) 1948.

42. Vogelsang, T. M.: The Harris Slide Test: A Micro-Flocculation Test for Syphilis with Cardiolipin Antigen, Brit. J. Ven. Dis. **23**:109 (Sept.) 1947.

43. Kline, B. S.: Development of a Single Standard Slide Test for Syphilis, Am. J. Clin. Path. **18**:185 (March) 1948.

44. Giordano, A. S.; Culbertson, C. S., and Higgenbotham, M. W.: Cardiolipin Antigens in Serologic Tests for Syphilis, Am. J. Clin. Path. **18**:193 (March) 1948.

45. Andujar, J. J.; Anderson, M. M., and Mazurek, E. E.: Cardiolipin Blood Tests in Syphilis, Am. J. Clin. Path. **18**:199 (March) 1948.

46. Levine, B.; Kline, B. S., and Suessenguth, H.: Clinical and Serologic Evaluation of 27,103 Consecutive Slide Tests with Cardiolipin-Lecithin Antigen and Kline Antigen, Am. J. Clin. Path. **18**:212 (March) 1948.

47. Widelock, D.: The VDRL Slide Test, Am. J. Clin. Path. **18**:218 (March) 1948.

48. Bohls, S. W., and Shaw, P.: Cardiolipin Kolmer Antigen in Testing Icteric Syphilitic Serums, Am. J. Clin. Path. **18**:253 (March) 1948.

49. Rein, C. R., and Coren, R. S.: The Newer Serologic Tests for Syphilis, Rev. cubana de lab. clin. **1**:112, 1947.

50. Brown, R.: A Quantitative Macroprecipitation Test for Syphilis with the Cardiolipin-Lecithin-Cholesterol Antigen, Am. J. Syph., Gonor. & Ven. Dis. **31**:304 (May) 1947.

article by Levine's group, while devoid of statistical accuracy, indicates that a cardiolipin flocculation test yields fewer false positive results in normal persons and in persons with miscellaneous infections than do the standard Kline procedures.

In leprosy, on the other hand, cardiolipin antigen gives about the same number of false positive reactions as do other tests (Rein and Coren [49]).

Stout [51] found that cardiolipin, as used in the Kolmer complement fixation technic, provided 34 per cent of false positive or doubtful results in 115 malarial serums, as contrasted to only 19 per cent with the standard Kolmer antigen.

TABLE 2.—*False Positive Serologic Reactions in Various Conditions (Levine, Kline and Suessenguth)* [46]

| | Cardiolipin | Kline Diagnostic Test | Kline "Exclusion" Test * |
|---|---|---|---|
| Normal persons † | 20 | 58 | 83 |
| Miscellaneous diseases, including infectious mononucleosis and "viral respiratory infection" † | 36 | 71 | 117 |

* The number of persons in these several diagnostic categories is not given. For some, but not all, the number of tests performed is stated, but no data are supplied on possible multiple specimens from the same patient. Presumably, though it is not definitely stated by the authors, each specimen was examined by the three serologic technics named in the table.

† The quotation marks are supplied by the reviewers.

As to sensitivity, most workers agree with Rein and Coren [49] that, properly adjusted as to components, cardiolipin antigen is more sensitive (certainly on a quantitative basis) in syphilitic serums than are older antigens.

However, the hope that cardiolipin might permit the standardization of serologic testing for syphilis and the abandonment of the confusing claims for superiority of one or another of the older technics has not as yet been realized. As Mahoney [52] puts it editorially:

> Six years ago cardiolipin, as a new phospholipin component of antigen for serologic tests for syphilis, was announced. Clinicians and serologists welcomed this announcement for they hoped that this new substance would be the long-sought-for key to the simplification or, at least, to the clarification of the serology of syphilis. They thought that simplification would be achieved by the adoption of a few universally accepted procedures which would utilize cardiolipin. Thus, the innumerable procedures which used the lipoidal antigens would be eliminated.
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> But six years of experience shows that cardiolipin has neither simplified nor clarified the serology of syphilis. Cardiolipin antigens have been adapted to the

51. Stout, G. W.: Reactivity of Tests Using Cardiolipin Antigens in a Limited Number of Nonsyphilitic Cases, Am. J. Syph., Gonor. & Ven. Dis. **31**:314 (May) 1947.

52. Mahoney, J. F.: Cardiolipin, editorial, Am. J. Clin. Path. **18**:230 (March) 1948.

technics which formerly used lipoidal antigens. The number of technical methods has increased rather than decreased. These new methods are being used by ever increasing numbers of laboratories.

In the testing of large numbers of specimens from syphilitic individuals, the performance of cardiolipin antigens has been comparable to that of the older antigens; but as yet there has not been sufficient testing of material from diverse nonsyphilitic individuals to warrant any conclusion concerning the specificity of the modified procedures. Final appraisal of cardiolipin can be achieved only when it has been applied to a significant volume of authenticated, clinically diverse testing material. Perhaps this appraisal will be achieved from the analysis of the mass of data accumulating from the extensive testing now in progress. If not, then the measure of specific reliability must be determined by the more cumbersome procedure of original method evaluation studies.

To put it simply, although laboratory observations justify much optimism concerning the future of cardiolipin in serologic tests for syphilis, it has not been demonstrated that its use can remove any responsibility from the clinician who interprets the results of laboratory procedures in behalf of the patient for whom the tests are performed.

### PUBLIC HEALTH AND VENEREAL DISEASE CONTROL MEASURES

Guthe and Hume have written a long statistical article on the international aspects of venereal disease. Those interested in the subject should refer to the original article.[53]

Postwar control of venereal disease is discussed by Heller.[54] He presents a summary of progress toward the control of venereal disease. Ten years ago the number of deaths due to all forms of syphilis was estimated to be approximately 16 per 100,000 population per year in the United States; in 1946 it was 9.3 per 100,000. Ten years ago the number of infant deaths due to syphilis was 69 per 100,000 live births; it was 25 in 1945. Patients were admitted to mental hospitals as a result of syphilis at the rate of 7.1 per 100,000 in 1937; in 1944 the rate was 5.8 per 100,000 population per year.

Ten years ago Parran formulated nine basic principles of public health control of syphilis. These state the necessity of a trained public health staff, adequate case finding and case holding, premarital and prenatal serodiagnostic tests, adequate diagnostic laboratory services, adequate treatment facilities, free distribution of antisyphilitic drugs, routine serodiagnostic tests, scientific information programs and public education. Heller points out the remarkable advances made during the last decade in each of these modalities of public health control. Heller also briefly mentions the many extensive investigations into a wide variety of fundamental research problems which hold great potentialities for further real progress in the control of venereal disease.

53. Guthe, T., and Hume, J. C.: International Aspects of the Venereal Disease Problem, J. Social Hyg. **34**:51 (Feb.) 1948.

54. Heller, J. R., Jr.: Venereal Disease Control During the Post War Period, Am. J. Syph., Gonor. & Ven. Dis. **31**:569 (Nov.) 1947.

Hilleboe [55] emphasizes the need for continued cooperation between private physicians and public health agencies as exemplified by the systematic reporting and follow-up of infected persons separated from the armed forces during the period of demobilization. He continues:

> The most striking progress in venereal disease control has been made in therapy, with the development of rapid treatment methods for both syphilis and gonorrhea. The network of rapid treatment facilities established by the Public Health Service as an emergency measure is now being taken over by the states for permanent peacetime use. We have also gained much experience in case-holding, in contact investigation and in mass case-finding on a scale considered visionary only a few years ago.

*Legislation for Venereal Disease Control in Germany.*—"Next to the fight against tuberculosis the combatting of venereal disease is the most important public health problem in Germany today." This has been recognized by the Allied Control Council, the quadripartite government of Germany, the existence of which is presently the subject of world-wide political discussions.

In a recent draft law, published as an appendix to Control Council Directive 52, the Control Council,[56] "taking into consideration the increasing incidence of venereal disease among the German population, and in the interest of health conditions in Germany," adopted a uniform plan and procedure in all the zones of occupation of Germany for the fight against venereal disease among the German population.

*Syphilis and Prostitution.*—Rosenthal and Kerchner [57] present an analysis of the results of examination of women arrested on prostitutional charges in New York city for the period 1936 to 1946. From 1936 to 1944 there was a decline in the percentage of these women found to have late syphilis but an actual increase in 1945 and 1946. Since 1940, however, the incidence of early syphilis in this group has steadily increased from 0.1 per cent in 1940 to 1.0 per cent in 1946. This exceeds the observed increase in early syphilis in the general population which has been noted in this area and other parts of the country since 1941.

*Infant Deaths from Syphilis.*—Brewer and Olson [58] record a decrease in infant deaths in California due to syphilis from 51 in 1938, the year before compulsory prenatal blood testing went into effect, to 28 in 1945. The infant mortality rate for syphilis per 1,000 live births

55. Hilleboe, H. E.: The United States Public Health Service and the Private Practice of Medicine, Illinois M. J. **92**:272 (Nov.) 1947.

56. Venereal Disease Control Legislation in Germany, Foreign Letters (Berlin), J. A. M. A. **137**:660 (June 12) 1948.

57. Rosenthal, T., and Kerchner, G.: Venereal Disease in Prostitutes, Am. J. Syph., Gonor. & Ven. Dis. **32**:256 (May) 1948.

58. Brewer, A. F., and Olson, F. E.: Evaluation of California's Law of Requiring a Prenatal Serologic Test for Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:633 (Nov.) 1947.

decreased from 0.50 in 1938 to 0.15 in 1945. The case rate for congenital syphilis per 1,000 live births dropped from 1.60 in 1938 to 0.54 in 1945. It is not clear how much of these reductions were due to this law and how much to other measures.

*Contact Investigation.*—Examining the success of contact investigation data from state and local health departments, Iskrant, Kahn and Rion outline a statistical method for evaluating contact investigation used by the Office of Statistics of the Venereal Disease Division of the United States Public Health Service. The first article [59] indicates the wide variations in methods of analysis in contact investigation employed by health departments and describes a standardized method which provides for several indexes as follows: (*a*) "epidemiologic index," i. e., the ratio of the number of infected persons identified through contact investigation to the number in whom syphilis was diagnosed; (*b*) "brought-to-treatment index," the ratio of hitherto unknown cases found through contact investigation to original patients available for interview; (*c*) "lesion-to-lesion index," the ratio of contacts of persons with primary or secondary syphilis brought to treatment as a result of contact investigation of patients with early infectious syphilis. In the second article, Iskrant and Rion [60] describe achievements in this field in the United States. Some health departments have achieved a creditable level of performance, though there is still much room for improvement. While the trend of achievement is generally upward, this is not steady, and constant effort is demanded. In twenty-one areas of the United States the epidemiologic index determined by the authors' method ranged from a minimum of 0.09 to a maximum of 1.19. The latter figure represents, of course, a highly creditable accomplishment.

Lamb, Kiesselbach and Morse [61] attempted to measure the effectiveness of an intensive educational venereal disease case-finding demonstration conducted from October 16 through November 30, 1946, by the Louisville-Jefferson County Board of Health in cooperation with the Kentucky State Department of Health and the United States Public Health Service. A campaign of public education, including the press,

59. Iskrant, A. P., and Kahn, H. A.: Statistical Indices Used in the Evaluation of Syphilitic Contact Investigation, J. Ven. Dis. Inform. **29**:1 (Jan.) 1948.

60. Iskrant, A. P., and Rion, J. W.: Status of Contact Investigation: An Evaluation of Data from State and Local Health Areas, J. Ven. Dis. Inform. **29**:7 (Jan.) 1948.

61. Lamb, W. F.; Kiesselbach, M. R., and Morse, J. W.: Louisville-Jefferson County Venereal Disease Case-Finding Demonstration, J. Ven. Dis. Inform. **29**:67 (March) 1948.

radio and outdoor advertising mediums, was used to familiarize the community with the symptoms and dangers of syphilis and gonorrhea. The opportunity for immediate diagnosis and treatment was emphasized. The case-finding demonstration was given further impetus by private physicians, to whom free penicillin was given for the treatment of patients with gonorrhea and early syphilis.

The project was designed to induce persons who believed they were infected to seek examination from the health department or from a private physician. Approximately 7,800 persons were examined, of whom 41.2 per cent were found to be infected. This included persons previously treated. The total number of patients examined was more than four times the number routinely examined in the same time period prior to the campaign. During the twelve months before the project, only 6 cases of primary and secondary syphilis and 49 of gonorrhea were reported by private physicians, whereas during the forty-five days of the project, 20 cases of primary and secondary syphilis and 415 of gonorrhea were so reported.

The results achieved by the Chattanooga-Hamilton County Health Department in investigating contacts of patients with early syphilis have been reported by von Werssowetz.[62] There were 3,383 contacts in the study, divided into (*a*) 1,250 contacts of patients with primary and secondary syphilis and (*b*) 2,133 contacts of patients with early latent syphilis. Of the former group, 927 (74.1 per cent) were examined; 271 (21.7 per cent) were already under treatment and therefore did not represent previously untreated patients with syphilis found through investigative efforts. Of the remaining 656 contacts examined, 338 (51.5 per cent) were found not to be infected with syphilis. A diagnosis of previously untreated syphilis was made for 318 (48.5 per cent) of this group. These patients were further divided into 142 with primary and secondary syphilis, 131 with early latent syphilis and 45 with late manifestations of the disease.

Of the 2,133 contacts of persons with early latent syphilis, 363 (17 per cent) were already under treatment. Exclusive of those already under treatment, contact investigations therefore brought in for examination 1,101 persons. Of these, 655 (59.5 per cent) were found not to be infected. Four hundred and forty-six (40.5 per cent) did have syphilis. In this group, however, there were only 43 cases of primary and

62. von Werssowetz, A. J.: The Incidence of Infection in Contacts of Early Syphilis, J. Ven. Dis. Inform. **29**:132 (May) 1948.

secondary syphilis (3.9 per cent of the total contacts examined). A diagnosis of early latent syphilis was made in 265 cases and of late syphilis in 138 cases. In view of these data, the writer does not agree with the suggestion that all contacts of patients with primary and secondary syphilis be treated for syphilis irrespective of the presence or absence of proved infection.

From March 31 through July 8, 1947, Easley, Parkhurst and Swank [63] undertook a field experiment to determine the results obtainable in three Arkansas counties by intensification of a program of contact investigation of early syphilis. Without the employment of additional personnel, a sixfold improvement was made during this time period over the previous over-all results of contact investigation, and almost eight times as many persons with early infectious syphilis were found as had been brought to treatment by earlier operations.

In order to evaluate the effectiveness of syphilis control measures, it is essential to have some index by which the trend of incidence and prevalence of the disease can be measured. Data for this index should be derived from cross sections of the population which are comparable biologically and susceptible of reduplication from year to year. Such an area is the Eastern Health District of Baltimore, in which detailed studies of incidence and prevalence (many of which have been previously noted in these reviews) have been under way for a decade. In the most recent of these studies, Leiby and his fellow workers [64] point out that an index of prevalence may be found in the amount of syphilis among parturient women. Year after year the natural physiologic process of pregnancy selects essentially similar groups of persons from the general population of a community and the prevalence of syphilis among this relatively small group may be used as an indication of the trend of syphilis in a given area. When this index was used within an area in which active syphilis control measures are practiced and in which ample facilities for antisyphilitic therapy are available, it was found that prevalence rates of syphilis among either the white or the Negro population for the two time periods studied had not significantly changed from 1937 to 1940 inclusive.

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63. Easley, E. J.; Parkhurst, G. E., and Swank, R. R.: The One Hundred-Day Experiment in Contact Investigation in Arkansas, J. Ven. Dis. Inform. **29**:13 (Jan.) 1948.

64. Leiby, G. M.; Turner, T. B.; Clark, E. G.; Dyar, R., and Kluth, F. C.: Studies on Syphilis in the Eastern Health District of Baltimore City: IV. Syphilis Among Parturient Women as an Index of the Trend of Syphilis in the Community, Am. J. Hyg. **46**:260 (Sept.) 1947.

PROGNOSIS OF SYPHILIS

*Syphilis and Life Insurance.*—Moore and Schamberg [65] discuss the important problem of the eligibility for life insurance of syphilitic persons. The usual actuarial approach is to compare the mortality rate in a group of known syphilitic patients with that in the population as a whole or in a select group of supposedly healthy persons. Data so obtained indicate that syphilis presumptively imposes an extra mortality hazard ranging from 138 to 188 per cent of expected mortality. All such studies to date are, to an undeterminable extent, inaccurate and inadequate to permit formation of a sound policy determining the insurability of syphilitic persons for the following reasons:

1. The known syphilitic population is compared with a supposedly nonsyphilitic population, the latter of which, however, contains an unknown proportion of persons with actuarially unrecognized syphilis.

2. The published mortality data (in a syphilitic population) consider as a group persons with all stages and types of syphilitic infection, ranging from recently acquired (primary and secondary) syphilis, to various grave forms of late syphilis (e. g., cardiovascular and neurosyphilis). . . .

3. The exact mortality due primarily or even secondarily to syphilis is not determinable from the causes of death provided on death certificates. . . .

4. Consideration is not given to the weighting of syphilis mortality figures by the fact that syphilis is primarily a disease of those in lower socioeconomic groups, which are subject to increased mortality risk from many other diseases and conditions. . . .

5. Consideration is not given to the adequacy of present day treatment methods. . . .

It must be concluded, therefore, that actuarial studies of the mortality of syphilis so far made are incomplete, inaccurate and unsuitable for the determination of a policy in regard to the insurability of syphilitic persons. Further studies are urgently required, the character and scope of which should be determined by a conference group of clinicians and actuarial experts.

The authors say that three alternative policies as to syphilis in applicants would appear to be open:

1. To disregard altogether the factor of syphilis, on the grounds that (*a*) less than 10 per cent of applicants (percentage varying on the basis of race, sex, age, socioeconomic status and geographic location) are infected at the time of application; (*b*) in those who show clinical or laboratory evidence of the disease at the time of application, or who admit a history of infection or of treatment for it, the overall increased mortality hazard may be disregarded, since (*c*) in those without clinical or laboratory evidence of infection, or who deny its previous existence, a

65. Moore, J. E., and Schamberg, I. L.: The Eligibility of Syphilitic Persons for Life Insurance, J. A. M. A. **134**:1532 (Aug. 30) 1947.

substantial number are nevertheless already actually infected but are medically unrecognized as having the disease; some are deliberately concealing the fact or will become infected after insurance is granted, thereby increasing the hazard in the supposed nonsyphilitic group to a point approaching that in the syphilitic group.

2. To require, as at present, the routine questioning of all applicants as to the existence of syphilis; and in addition to insist on a routine blood serologic test for syphilis of all applicants.

3. To continue, as at present, to decide individually the question of insurability of all persons in whom syphilis is recognized by clinical or laboratory evidence or by history and to ignore the factor of syphilis in all others, with full knowledge that the latter group will nevertheless contain a substantial proportion of infected persons.

Each of these alternatives is open to several objections. The first would unquestionably impose a slight but definite increase in the overall actuarial risk, by the inclusion of persons with definitely or probably fatal forms of the disease.

The second, requiring routine serologic testing of all applicants, would add materially to the cost of examination and, especially in the case of the Veterans Administration, would impose the difficult and in some cases nearly impossible task of differentiating biologic false positive serologic tests from those actually due to syphilis.

Because of these objections to the first two alternatives, the third (in spite of its obvious medical and actuarial drawbacks and the premium which it places on concealment of disease on the part of applicants) will probably continue in force.

If either the second or the third alternative is chosen, the question arises of what shall be done with the applicant in whom syphilis is detected. The following suggestions are made:

1. No applicant with untreated syphilis in any stage should be granted insurance if, as with commercial companies, the applicant must demonstrate good health.

2. If treatment has been given, it should have been adequate. In this connection, the term adequate is used to describe the amount and character of treatment which is sufficient to cure the majority of patients in a particular phase of syphilitic infection. It is recognized that many individual patients may have been cured with less than this average amount, while others may not have achieved cure with much more. If an applicant has received less than the average adequate amount, and even though he may appear cured as a result thereof, he should be required to complete the average amount of treatment before insurance will be granted. The standard of adequacy is a constantly changing one, and too rigid requirements should not be laid down.

3. In certain phases of syphilitic infection, though not in all, a period of observation following treatment should be required, in order to demonstrate the probability of cure.

### EARLY SYPHILIS

*Chancre.*—One of the most widespread misconceptions in the medical profession is that the primary lesion of syphilis is invariably single. In

one year Kuhl and Boggs [66] studied 652 patients with primary syphilis. The chancres were single in 378 (58 per cent), multiple in 251 (38.5 per cent) and indeterminate in 23 (3.5 per cent). Of the extragenital chancres encountered in the series, only one example of multiple lesions was seen ("kissing lesions" of the lips).

*Generalized Lymph Node Enlargement.*—During the performance of routine physical examinations on naval personnel, Moorman [67] noted that palpable lymph nodes were commonly found in the cervical, axillary and inguinal regions. One hundred healthy white men without history of recent illness or of syphilis, most in the third decade of life, were examined carefully for palpable nodes. Anterior and posterior cervical nodes were palpable in 21 and 19 per cent respectively, axillary in 76 per cent, epitrochlear in 11 per cent, superficial inguinal in 84 per cent and superficial subinguinal in 72 per cent. In the majority of instances the nodes were 1 cm. or less in diameter. These data should enjoin caution in the use of the phrase "generalized lymph node enlargement" by the syphilologist.

*Leukocyte Count in Early Syphilis.*—Willcox [68] points out that writers in the fields of hematology and syphilology have said that leukocytosis, eosinophilia and absolute lymphocytosis or monocytosis are frequent in patients with untreated early syphilis. These statements were not borne out by his investigation of the total and differential white blood cell counts in 405 young white men with primary or secondary syphilis. The mean total count for the entire group was 8,950 leukocytes per cubic millimeter. The differential picture was normal.

*Relapse Versus Reinfection in Early Syphilis.*—The extreme clinical difficulty in differentiation between relapse and reinfection in treated early syphilis accounts for the fact that practically all investigators of the penicillin treatment of early syphilis have included patients in these two categories as "treatment failures." This is in spite of the fact that many workers are convinced that the incidence of reinfection after the penicillin therapy of early syphilis is high and may indeed account for perhaps half of the supposed clinical failures observed. Schamberg and Steiger [69]

66. Kuhl, I. W., and Boggs, H.: The Incidence of Multiple Lesions in Primary Syphilis, New England J. Med. **238**:399 (March 18) 1948.

67. Moorman, W. W.: Incidence of Palpable Lymph Nodes, U. S. Nav. M. Bull. **47**:821 (Sept.-Oct.) 1947.

68. Willcox, R. R.: The White Cell Count in Early Syphilis of Males, J. Roy. Army M. Corps **90**:61 (Feb.) 1948.

69. Schamberg, I. L., and Steiger, H. P.: Syphilitic Relapse Versus Reinfection, J. Ven. Dis. Inform. **29**:92 (April) 1948.

examine the problem of clinical differentiation of such patients on the basis of six multiple infectious syphilitic episodes in married couples ("ping-pong syphilis"). They believe that reinfection is recognizable with reasonable certainty if (*a*) clinical evidence of a second infection precedes serologic evidence, (*b*) there is similarity in clinical and serologic response of the first and supposed second infections to each identical treatment course and (*c*) epidemiologic evidence can be provided showing that there has been sexual exposure, after treatment of the original patient, with a person who has been examined and diagnosed as having infectious syphilis; if the presence of infectious lesions in the contact at the time of intercourse with the patient can be verified, and, further, if there is an appropriate incubation period between the time of sexual exposure with the infectious contact and the reappearance of lesions in the patient. Agreeing, however, that these data are not always available, Schamberg and Steiger suggest the term "infectious syphilitic episode" as a noncommittal diagnosis when differentiation between relapse and reinfection does not seem possible.

*Gastric Syphilis Associated with Early Syphilis.*—Schwartz [70] compared 12 patients with secondary syphilis with 3 nonsyphilitic persons having superficial gastritis in regard to the state of the gastric and rectal mucosae as seen by gastroscopy and sigmoidoscopy, derangement in gastric secretions and the response of these factors to administration of penicillin. The gastroscopic picture was similar to that of chronic superficial gastritis with hyperemia, edema and adherent mucous patches indistinguishable from those seen in the mouth and rectum. Penicillin therapy (2,400,000 units in 7.5 days) produced rapid amelioration of mucosal inflammation in 10 of the 12 patients; no change was seen in the 3 control patients. Hypochlorhydria was found in 9 and histamine-refractory achlorhydria in 3 of the study patients prior to therapy. After treatment, 7 showed normal acid values, 4 remained hypochlorhydric and 1 slowly changed from the achlorhydric to the hypochlorhydric state.

Lyman,[71] basing his opinion on gastroscopic examinations on 130 patients with secondary syphilis, emphasizes that in the majority of cases it is extremely difficult, if not impossible, to determine by appearance alone the etiologic role of early syphilis in gastric ulcerations.

*Electrocardiographic Changes in Early Syphilis.*—Steiger and Edeiken [72] made electrocardiographic studies on 30 patients with dark

70. Schwartz, I. R.: Gastroscopic Observations in Secondary Syphilis, Gastroenterology **10**:227 (Feb.) 1948.

71. Lyman, R., in discussion on Patterson and Rouse,[73] p. 483.

72. Steiger, H. P., and Edeiken, J.: Electrocardiographic Changes in Early Syphilis, Am. Heart J. **34**:674 (Nov.) 1947.

field–positive primary or secondary syphilis. Electrocardiograms were obtained before treatment and at three day intervals thereafter. A control series consisted of 8 patients given a comparable amount of penicillin for diseases other than syphilis. There was no clinical evidence of heart disease in any. Fifteen of those with early syphilis showed electrocardiographic abnormalities consisting of changes in the T waves and RS-T segments in the limb and/or chest leads. There was no relationship between these changes and Herxheimer reactions or the amount of penicillin received. In some instances the electrocardiographic changes were transient, but in others they lasted for several months. The authors suggest that the electrocardiographic anomalies noted may be due to changes within the heart muscle. The lack of autopsy material and the decided differences of opinion of pathologists as to cardiac changes in early syphilis make this suggestion a fertile field for speculation.

### LATE SYPHILIS

*Late Syphilis of the Stomach.*—Patterson and Rouse [73] point out that although syphilis of the stomach seems to be a disappearing disease, nevertheless it must be considered in the differential diagnosis of gastric lesions in patients with late acquired syphilis. The lesions in the stomach are variably ulcerated, noduloulcerated, nodular, infiltrating or fibrosing and may involve only segments (usually the lower third) or almost the entire stomach. They personally studied 14 patients diagnosed as having untreated gastric syphilis. The lesions appeared to be ulcerating and ulceronodular in 8, nodular or gummatous tumor without ulceration in 3 and infiltrative or leather bottle plastic linitis in 3 patients. The livid hue of the mucosal margins about the syphilitic ulcer on gastroscopy appears somewhat different from the often comparatively normal pink color of the gastric mucosa about a peptic ulcer or the fiery red, highly vascular margins of an ulcerating carcinoma of the stomach. The borders of syphilitic lesions, they say, tend to be serpiginous and the ulcers large, irregular and shallow.

*Aortitis.*—Since the serious late manifestations of cardiovascular syphilis probably result from the invasion by Treponema pallida of the small vessels supplying the aorta and other great vessels, a study by Schlichter [76] has particular application in the field of syphilis. By means

73. Patterson, C. O., and Rouse, M. O.: Description of Gastroscopic Appearance of Luetic Gastric Lesions in Late Acquired Syphilis, Gastroenterology **10**:474 (March) 1948.

74. Deleted by author.

75. Deleted by author.

76. Schlichter, J. G.: Vascularization of the Aorta in Different Species in Health and Disease, Am. Heart J. **35**:850 (May) 1948.

of an injection technic with a radiopaque mixture, he studied the vascularity of the aorta in the dog, chicken, rabbit and man. The most pronounced vascularity was found in dogs, the next in man and the least in rabbits. In dogs, extensive adventitial and less extensive medial plexuses are joined by vasa which arise from the lumen of the aorta. The adventitial plexus becomes less extensive as one progresses from the ascending to the descending aorta. No intimal plexus could be visualized. In other species studied, the adventitial plexus alone was found. Schlichter thinks that vascularization of the aorta, which varied widely in different species, is a decisive factor in localization and may play a role in the development of atheromatous lesions.

Thorner and Carter [77] reviewed the incidence of aortic calcification in all cases of syphilitic aortitis which came to autopsy at the Los Angeles County General Hospital from 1939 to 1946. Calcification was roentgenologically identified in the thoracic aorta in 37 of 111 cases (33.3 per cent), with involvement of the ascending aorta in 16 cases (14.4 per cent).

*The Effect of Treatment on the Pathologic Picture in Syphilitic Aortitis.*—Surprisingly few comparisons of the pathologic picture in treated and untreated syphilitic aortitis are available in the literature. Hood and Mohr [1d] in 1937 compared two groups of 17 patients each, one of which had received eight months' or more continuous treatment with arsenicals or bismuth and the other no therapy. They concluded that there was no difference between the microscopic appearance of the aorta in the treated and untreated groups when the duration of infection was taken into account. This was also the impression of Chapman and Morgan.[78] On the other hand, Howe in 1943, on the basis of a study of 17 cases, concluded that the amount of cellular infiltration in the aortic wall bore an inverse relationship to the amount of arsenical therapy received.

The present report of Webster and Reader [79] tends to confirm the findings of Howe and is diametrically opposed to the findings of Hood and Mohr and of Chapman and Morgan. In the current study, microscopic sections of the aortas of 45 patients with evidence of syphilitic

77. Thorner, M. C., and Carter, R. A.: The Roentgenologic Diagnosis of Syphilitic Cardiovascular Disease, Am. Pract. **2**:301 (Jan.) 1948.

78. Chapman, D. W., and Morgan, R. H.: Syphilitic Cardiovascular Disease: An Analysis of Fifty-Nine Cases of Aortic Aneurysm and a Review of Modern Concepts of Treatment, Am. Pract. **2**:159 (Nov.) 1947.

79. Webster, B., and Reader, G. G.: The Effect of Antisyphilitic Treatment on the Microscopic Appearance of Syphilitic Aortitis, Am. J. Syph., Gonor. & Ven. Dis. **32**:19 (Jan.) 1948.

aortitis were examined. The degree of inflammation was recorded on a scale rated according to the intensity of the perivascular infiltration, endarteritis, lymphocytic infiltration and the presence of plasma cells. It was found that only 3 of 19 "adequately" treated patients showed active inflammation, whereas all of 19 untreated patients showed an active syphilitic process, 1 presenting notable endarteritis and a microscopic gumma. Five of 7 who had received "inadequate" treatment showed pathologically active inflammation. No correlation was demonstrable between duration of infection and activity of the aortitis. The authors feel that "adequate" therapy for syphilitic aortitis profoundly modifies the inflammatory process in the aortic wall. It is worthy of note, however, that 10 of 19 untreated and 7 of 19 "adequately" treated patients died as a result of cardiovascular syphilis and that this difference is not statistically significant.

*The Asymptomatic Phase of Syphilitic Aortic Insufficiency.*—In a paper remarkable for the statistical confusion which can occur even with small numbers, Reader, Romeo, Webster and McDermott [80] report further observations on 43 patients with syphilitic aortic regurgitation followed for two to sixteen years. Within these time limits, 13 of the 43 had died, 8 of heart disease and 5 of other causes. As nearly as the reviewers can determine from the data as presented, among 27 patients in whom the cardiac lesion five and a half years previously was wholly asymptomatic or "symptomatic on questioning only," the status of only 7 had changed for the worse. Nevertheless, 26 of these 27 patients were still well compensated despite the duration of aortic insufficiency (six to twelve years), and 12 of them remained completely asymptomatic. The subjective statements of the patients were confirmed by various objective examinations including determination of the circulation time, venous pressure, vital capacity, cardiothoracic ratio and blood pressure. The authors reaffirm their previous opinion that too grave a prognosis is usually given for syphilitic aortic insufficiency and that this form of heart disease is characterized by an asymptomatic phase which may last two to ten years and by a symptomatic phase which may last two to fourteen years. They think that prolonged circulation time and low diastolic blood pressure offer the best prognostic indexes. All their patients were intensively treated with metal chemotherapy, and their data add little information on the natural course of syphilitic heart disease.

80. Reader, G. G.; Romeo, B. J.; Webster, B., and McDermott, W.: The Prognosis of Syphilitic Aortic Insufficiency, Ann. Int. Med. **27**:584 (Oct.) 1947.

NEUROSYPHILIS

*Primary Optic Atrophy.*—If not properly treated, unilateral syphilitic primary optic atrophy always becomes bilateral. Bruetsch [81] has autopsy information on 12 cases of syphilitic primary optic atrophy; in 2 of the cases death had occurred at a time when the atrophy was still confined to one eye. Histologic study of the visual pathways in these 2 cases furnished the clue to the ultimate degeneration of the nerve fibers of both optic nerves. When demyelination of the nerve fibers had progressed to complete degeneration in one optic nerve, there was already present in the not yet demyelinated optic nerve a syphilitic inflammatory exudate which ultimately would lead to atrophy.

In a second excellent paper [82] dealing with the long-standing argument concerning the advisability of surgical measures in primary optic atrophy, Bruetsch discusses the subject of syphilitic optochiasmatic arachnoiditis. He summarizes as follows:

Recent theories have attributed the cause of primary syphilitic atrophy of the optic nerves to syphilitic optochiasmatic arachnoiditis, and surgical intervention has been recommended. On the basis of a histologic study of 12 cases of syphilitic primary atrophy of the optic nerves, the propriety of surgical intervention is discussed.

In 4 cases of syphilitic atrophy of the optic nerves no arachnoidal adhesions were present at all, and in 2 other cases the slight arachnoidal thickening could be considered as still within normal limits. In the other 50 per cent of cases there was definite syphilitic arachnoiditis in the optochiasmatic region. In these cases the pronounced thickening of the arachnoid, burying the optic nerves, the chiasm and, at times, the third and other cranial nerves, suggested from the gross appearance alone that the arachnoidal process could be implicated in the atrophy of the optic nerves. Microscopic examination corrected this erroneous impression, revealing that the thickened arachnoid passed harmlessly over the optic nerves and chiasm, leaving no signs of pressure, such as constrictive grooves in the optic nerves.

Primary syphilitic optic nerve atrophy is essentially the result of an inflammatory process in the intracranial portion of the optic nerves and in the chiasm. The inflammation has its origin in a basilar syphilitic meningitis, which in some instances produces an optochiasmatic arachnoiditis and in others leaves the basilar arachnoid grossly unaltered.

Surgical removal of the arachnoidal adhesions will be of little, if any, benefit because the inflammatory process within the optic nerves and chiasm remains unaltered by the operative procedure.

The most efficacious treatment of primary syphilitic optic nerve atrophy at the present time is malarial therapy, aided by a course of concomitant and subsequent injections of penicillin, with 5,000,000 units in each course.

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81. Bruetsch, W. L.: Unilateral Syphilitic Primary Atrophy of the Optic Nerves: An Anatomic Study of Two Cases, Arch. Ophth. **39**:800 (Jan.) 1948.

82. Bruetsch, W.: Surgical Treatment of Syphilitic Primary Atrophy of the Optic Nerves (Syphilitic Optochiasmatic Arachnoiditis), Arch. Ophth. **38**:735 (Dec.) 1947.

Levin, Trevitt and Greenblatt [83] present an analysis of 54 patients with syphilitic primary optic atrophy seen at the Boston Psychopathic Hospital between 1921 and 1944. Only 3 were females. In 34 (63 per cent) the first clinical manifestation of neurosyphilis was gradual loss of vision. From the neuropsychiataric standpoint, 29 were patients with predominant signs of dementia paralytica, and in 25 the tabetic element was more marked. In general, these clinical manifestations were not far advanced at the time of ophthalmologic diagnosis.

Of 43 patients not totally blind at the initiation of treatment, 27 were followed two years or more (mean time, seven years). Of 11 patients given chemotherapy only, 6 were blind on follow-up examination after two years or longer. Of 16 patients treated with induced fever therapy in addition to chemotherapy, only 2 (13 per cent) were blind on follow-up examination two or more years later. These results confirm superior effects with the combined method. However, even combined fever-drug therapy must be begun before useful vision is lost; the most that treatment can do is arrest the process, and restoration of vision is not to be anticipated.

*Dementia Paralytica.*—Solomon, Rose and Arnot [84] have treated 13 patients with dementia paralytica with electric shock therapy. Five cases are briefly described. Satisfactory results were obtained in 3. A full analysis of the 13 cases is not presented. The authors believe that many of the psychotic manifestations of dementia paralytica are not anatomically determined. Patients with dementia paralytica who have prominent affective components in the psychosis respond well to electric shock, even though other signs and symptoms of organic brain disease may be present. Electric shock therapy is useful in some of the psychoses of dementia paralytica, especially in patients with states of extreme overactivity, when the quieting effect of shock may occasionally be life saving.

### PATHOLOGY OF SYPHILIS

Rosahn has collected the several reports published by himself and Black-Schaffer under the general title of "Autopsy Studies in Syphilis." [85] These papers have been referred to in past reviews. With modifications and additions, this monograph presents the results of the entire exhaustive study conducted by them from 1940 through 1946 at the Yale University School of Medicine and the laboratories of the New Britain

83. Levin, S.; Trevitt, L. D., and Greenblatt, M.: Syphilitic Primary Optic Atrophy: A Review of Fifty-Four Cases, New England J. Med. **237**:769 (Nov. 20) 1947.

84. Solomon, H. C.; Rose, A. S., and Arnot, R. E.: Electric Shock Therapy in General Paresis, J. Nerv. & Ment. Dis. **107**:377 (April) 1948.

85. Rosahn, P. D.: Autopsy Studies in Syphilis, J. Ven. Dis. Inform., 1948, supp. 21.

General Hospital. The work is especially important, since it demolishes the Warthin concept of the pathology of syphilis, which has dominated syphilologists for a quarter of a century. It is clearly shown that the so-called Warthin lesion is a part of the aging process, in syphilitic and nonsyphilitic persons alike.

Among 22 previable infants (weighing from 500 to 999 Gm.) examined pathologically by Arey [86] between October 1945 and May 1946, the immediate cause of death was congenital syphilis in 5. Four of these died within the first twenty-four hours and the fifth infant on the second day of life. Although the series is not large, the appalling incidence of syphilis in this group demonstrates the continued importance of syphilis as a public health problem, even though drugs are available which may be potentially capable of eradicating the disease.

86. Arey, J. B.: Postmortem Observations in Twenty-Two Premature Infants, New Orleans M. & S. J. **100**:258 (Dec.) 1947.

*(To Be Concluded)*

# News and Comment

## GENERAL NEWS

**Postgraduate Courses in Gastroenterology.**—The American College of Physicians announces postgraduate courses in gastroenterology at the University of California Medical School and Stanford University School of Medicine, San Francisco, Feb. 7 to 12, 1949. Some of the subjects to be covered are lesions of the mouth; diseases of the esophagus, stomach, small bowel, pancreas, liver and colon; peptic ulcer; cholecystic disease; gastrointestinal symptoms of cardiovascular origin; psychosomatic aspects of gastrointestinal diseases; early diagnosis of carcinoma of the gastrointestinal tract; recent advances in chemotherapy of malignant disease; physiology of bile pigment metabolism; drugs useful in therapy of gastrointestinal diseases; practical aspects of intestinal intubation; electrolyte and protein balance in patients with intestinal intubation; deficiency disease in the gastrointestinal tract, and gastrointestinal food allergy.

**Training Courses in Psychotherapy Announced.**—The Postgraduate Center for Psychotherapy, Inc., the training associate of the Institute for Research in Psychotherapy, Inc., has been granted a provisional charter from the Board of Regents of the New York State Educational Department. The center offers intensive training for psychiatrists in psychotherapy leading to certification and individual courses for general practitioners and nonpsychiatric medical specialists in psychotherapy and psychosomatic medicine.

# Book Reviews

**The Pathology of Nutritional Disease.** By Richard H. Follis Jr., M.D. Price, $6.75. Pp. 310. Springfield, Ill.: Charles C Thomas, Publisher, 1947.

This volume is a concise survey of the known pathologic changes in nutritional diseases. The author has selected his material carefully, reminding the reader that some phases of the early experimental work in nutritional deficiencies are not entirely accurate because multiple deficiencies were unknowingly being studied.

The book is divided into six parts, each one dealing with certain phases and groups of deficiencies. It begins with a general discussion of dietary deficiencies, followed by a survey of deficiencies in each of the essential elements. In this part, physiologic and pathologic effects of elemental deficiencies are described. Much of the data is derived from animal experimentation, and because deficiencies of single elements are not common in human beings these are not described extensively except in the instances of potassium, sodium, iron and iodine. The section on the essential amino acids is short and is concerned for the most part with experimental data. The largest and most extensive portion of the book deals with vitamins and their deficiencies. This is well documented and contains much useful information on both physiologic and pathologic effects of the deficiencies. A short survey of the essential fatty acids follows. The section on the pathologic anatomy of specific tissues in respect to nutritional deficiencies is excellent and summarizes well the associated organic changes in body tissues.

Dr. Follis makes use of an extensive bibliography, totaling 791 references. The illustrations are excellent. The work is a useful source of reference and information and adequately covers the subject of the pathology of nutritional diseases.

**Illustrative Electrocardiography.** By Julius Burstein, M.D., and Nathan Bloom, M.D. Third edition. Price, $6. Pp. 325. New York: D. Appleton-Century Company, Inc., 1948.

This book, now in its third edition, is one of the standard textbooks on electrocardiography. The subject is dealt with in the usual way: first, general discussion of principles; then, the various "waves," and finally discussion of the tracings in different diseases. The numerous excellent illustrations are a feature, but above all the book is a handy volume, not of undue weight or clumsy shape. There are also chapters on heart sound recording and on cardioradiology.

**Encyclopedia of Medical Sources.** By Emerson Crosby Kelly, M.D. Price, $7.50. Pp. 476. Baltimore: The Williams & Wilkins Company, 1948.

The pages of this book, closely printed in double column, are a sort of an index of prominent nineteenth and twentieth century physicians and scientists, with a key to their more important work. For example, under the name William Stewart Halsted, is found the word *Law*, followed by a definition of the principle brought out by Halsted that "transplanted tissue will grow only if there is a lack of tissue in the host." This in turn is followed by the appropriate journal reference. After this comes *Operation*, with a brief statement of the surgeon's principal contributions. The compilation is amazingly thorough, although it does not claim to be absolutely complete, and the surgeons are perhaps a little more comprehensively

dealt with than internists and others. This useful book points the way to a more definitive and encyclopedic treatise. The names are alphabetically arranged, and there is also an index of subjects.

**Semilogia cardiovascular.** By Rafael Carral y de Teresa, M.D. Pp. 499. México, D. F.: Instituto Nacional de Cardiología, 1948.

This book is devoted to the discussion of symptoms and signs of heart disease, and it is intended especially for the medical student and the practicing physician. The author has apparently written it to serve as a text for his courses at the University of Mexico.

The subject is treated in six parts. These are titled, "Functional Semiology," "Hemodynamics," "Semiology of Objective Signs," "Laboratory Examinations," "Radiological Semiology" and "Electrocardiographic Semiology." Each part is in turn divided into chapters in which the basic concepts involved are thoroughly discussed. A textbook pattern has been attained in order to permit unified discussions of the basic concepts and of the newer investigations and approaches. Presentations are included on some of the excellent works which have come from the Mexican National Institute of Cardiology, particularly in the fields of electrocardiography and cardiac roentgenology.

The book is well printed and illustrated and adequately fulfils its intended purpose. It is written in Spanish, but the material discussed is available in English medical publications.

**Factors Regulating Blood Pressure.** Transactions of the First Conference. Edited by B. B. Zweifach and Ephraim Shorr. Price, $1.90. Pp. 175. New York: Macy, 1947.

Since the advent of experimental work on hypertension, many noteworthy contributions have been made in this field. This monograph contains the transactions of the first conferences on the factors regulating blood pressure, and its purpose is to evaluate these contributions, to determine what has definitely been established and to clarify all important problems that remain to be pursued.

As the subject would indicate, hypertension may embrace many classifications, such as renal function, fluid balance and regulation of blood pressure under normal and pathologic conditions. Such notable persons as Harry Goldblatt, Arthur Grollman, Stanley E. Bradley and Irvine H. Page contribute greatly to the understanding of these problems, and by informal discussion after each presentation, a critical evaluation of the data is made.

Although no criteria are reached on which to judge the pathogenesis of human hypertension by all the work on experimental renal hypertension, it is felt that great benefit resulted from a summary and analysis of the experimental data to date. It is the hope of these authors that through the interchange of ideas an added impetus may result in which new ideas on the subject may be pursued.

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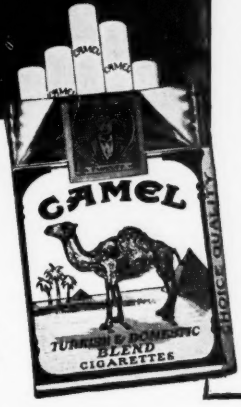


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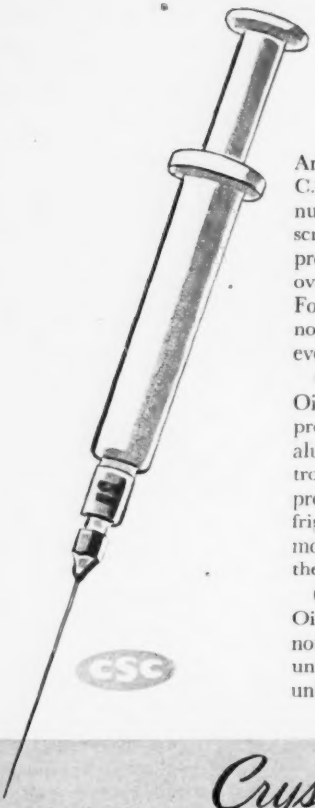


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